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**The PROMUS™ Everolimus Eluting Coronary Stent System  
Instructions for Use**



*Table of Contents*

- 1.0 PRODUCT DESCRIPTION
  - 1.1 Device Component Description
  - 1.2 Drug Component Description
    - 1.2.1 Everolimus
    - 1.2.2 Inactive Ingredients - Non-erodible Polymer
    - 1.2.3 Product Matrix and Everolimus Content
- 2.0 INDICATIONS
- 3.0 CONTRAINDICATIONS
- 4.0 WARNINGS
- 5.0 PRECAUTIONS
  - 5.1 General Precautions
  - 5.2 Pre- and Post-Procedure Antiplatelet Regimen
  - 5.3 Multiple Stent Use
  - 5.4 Brachytherapy
  - 5.5 Use in Conjunction with Other Procedures
  - 5.6 Use in Special Populations
    - 5.6.1 Pregnancy
    - 5.6.2 Lactation
    - 5.6.3 Gender
    - 5.6.4 Ethnicity
    - 5.6.5 Pediatric Use
    - 5.6.6 Geriatric Use
  - 5.7 Lesion/Vessel Characteristics
  - 5.8 Drug Interactions
  - 5.9 Immune Suppression Potential
  - 5.10 Lipid Elevation Potential
  - 5.11 Magnetic Resonance Imaging (MRI)
  - 5.12 Stent Handling
  - 5.13 Stent Placement
    - 5.13.1 Stent Preparation
    - 5.13.2 Stent Implantation
  - 5.14 Stent System Removal
  - 5.15 Post-Procedure
- 6.0 DRUG INFORMATION
  - 6.1 Mechanism of Action
  - 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent
  - 6.3 Interactions with Drugs or Other Substances
  - 6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

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EL2064613 (7/2/08)

Page 1 of 60

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- 6.5 Pregnancy
  - 6.6 Lactation
  - 7.0 OVERVIEW OF CLINICAL STUDIES
  - 8.0 ADVERSE EVENTS
    - 8.1 Observed Adverse Events
    - 8.2 Stent Thrombosis Definitions
    - 8.3 Potential Adverse Events
  - 9.0 SPIRIT FAMILY OF CLINICAL TRIALS
    - 9.1 SPIRIT III Pivotal Clinical Trial
      - 9.1.1 SPIRIT III Randomized Clinical Trial (RCT)
      - 9.1.2 SPIRIT III US 4.0 mm Arm
    - 9.2 SPIRIT II Supportive Clinical Trial
    - 9.3 SPIRIT FIRST Randomized Clinical Trial
    - 9.4 SPIRIT II and SPIRIT III Pooled Analysis
      - 9.4.1 Stent Thrombosis in SPIRIT II and SPIRIT III Pooled Analysis
      - 9.4.2 Diabetics in SPIRIT II and SPIRIT III Pooled Analysis
      - 9.4.3 Dual Vessel treatment in SPIRIT II and SPIRIT III Pooled Analysis
  - 10.0 INDIVIDUALIZATION OF TREATMENT
  - 11.0 PATIENT COUNSELING AND PATIENT INFORMATION
  - 12.0 HOW SUPPLIED
  - 13.0 OPERATOR'S INSTRUCTIONS
    - 13.1 Inspection Prior to Use
    - 13.2 Materials Required
    - 13.3 Preparation
      - 13.3.1 Packaging Removal
      - 13.3.2 Guide Wire Lumen Flush
      - 13.3.3 Delivery System Preparation
    - 13.4 Delivery Procedure
    - 13.5 Deployment Procedure
    - 13.6 Removal Procedure
    - 13.7 Post-Deployment Dilatation of Stent Segments
  - 14.0 *IN VITRO* COMPLIANCE INFORMATION
  - 15.0 REUSE PRECAUTION STATEMENT
  - 16.0 PATENTS
  - 17.0 WARRANTY

## 1.0 PRODUCT DESCRIPTION

The PROMUS™ Everolimus-Eluting Coronary Stent System (PROMUS EECSS or PROMUS stent system) is a private label XIENCE™ V Everolimus Eluting Coronary Stent System (XIENCE EECSS or XIENCE V stent system) manufactured by Abbott and distributed by Boston Scientific Corporation. The PROMUS V EECSS is a device/drug combination product consisting of either the MULTI-LINK VISION® Coronary Stent System or the MULTI-LINK MINI VISION® Coronary Stent System coated with a formulation containing everolimus, the active ingredient, embedded in a non-erodible polymer.

### 1.1 Device Component Description

The device component consists of the MULTI-LINK MINI VISION or MULTI-LINK VISION stent mounted onto the MULTI-LINK MINI VISION or MULTI-LINK VISION stent delivery system (SDS) respectively. The device component characteristics are summarized in Table 1-1.

**Table 1-1: PROMUS Stent System Product Description**

	PROMUS Rapid-Exchange (RX) EECSS	PROMUS Over-the-Wire (OTW) EECSS													
Available Stent Lengths (mm)	8, 12, 15, 18, 23, 28	8, 12, 15, 18, 23, 28													
Available Stent Diameters (mm)	2.5, 2.75, 3.0, 3.5, 4.0	2.5, 2.75, 3.0, 3.5, 4.0													
Stent Material	A medical grade L-605 cobalt chromium (CoCr) alloy MULTI-LINK VISION or MULTI-LINK MINI VISION stent														
Drug Component	A conformal coating of a non-erodible polymer loaded with 100 µg/cm <sup>2</sup> of everolimus with a maximum nominal drug content of 181 µg on the large stent (4.0 x 28 mm)														
Delivery System Working Length	143 cm	143 cm													
Delivery System Design	Single access port to inflation lumen. Guide wire exit notch is located 30 cm from tip. Designed for guide wires ≤ 0.014".	Sidearm adaptor provides access to balloon inflation/deflation lumen and guide wire lumen. Designed for guide wires ≤ 0.014".													
Stent Delivery System Balloon	A compliant, tapered balloon, with two radiopaque markers located on the catheter shaft to indicate balloon positioning and expanded stent length.														
Balloon Inflation Pressure	Nominal inflation pressure: 8 atm (811 kPa) for 2.5 and 2.75 mm diameters; 9 atm (912 kPa) for 3.0, 3.5, and 4.0 mm diameters Rated Burst Pressure (RBP): 16 atm (1621 kPa) for all sizes														
Guiding Catheter Inner Diameter		≥ 5 F (0.056")													
Catheter Shaft Outer Diameter (nominal)	<table style="width: 100%; text-align: center;"> <tr> <td><u>2.5–3.0 mm</u></td> <td><u>3.5–4.0 mm</u></td> </tr> <tr> <td>Distal: 0.032"</td> <td>0.035"</td> </tr> <tr> <td>Proximal: 0.026"</td> <td>0.026"</td> </tr> </table>	<u>2.5–3.0 mm</u>	<u>3.5–4.0 mm</u>	Distal: 0.032"	0.035"	Proximal: 0.026"	0.026"	<table style="width: 100%; text-align: center;"> <tr> <td><u>2.75 x 8 – 3.5 x 23 – 4.0 x 28</u></td> </tr> <tr> <td>Distal: 0.032"</td> <td>0.034"</td> <td>0.036"</td> </tr> <tr> <td>Proximal: 0.042"</td> <td>0.042"</td> <td>0.042"</td> </tr> </table>	<u>2.75 x 8 – 3.5 x 23 – 4.0 x 28</u>	Distal: 0.032"	0.034"	0.036"	Proximal: 0.042"	0.042"	0.042"
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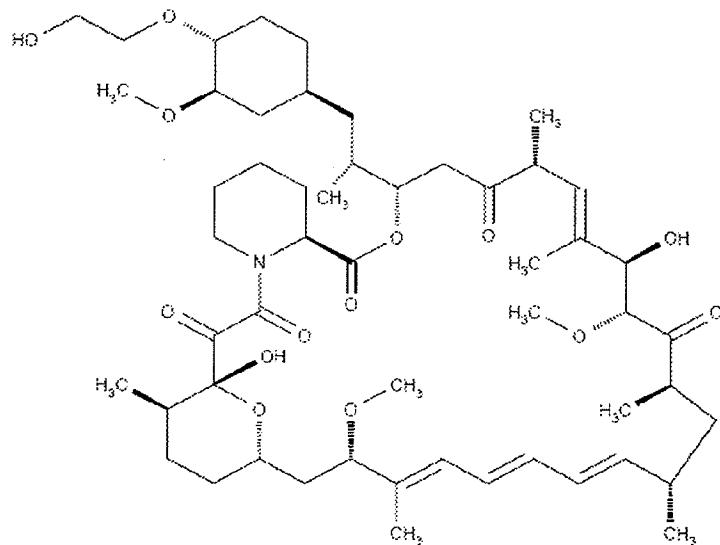
## 1.2 Drug Component Description

The PROMUS Everolimus- Eluting Coronary Stent (PROMUS stent) is coated with everolimus (active ingredient), embedded in a non-erodible polymer (inactive ingredient).

### 1.2.1 Everolimus

Everolimus is the active pharmaceutical ingredient in the PROMUS stent. It is a novel semi-synthetic macrolide immunosuppressant, synthesized by chemical modification of rapamycin (sirolimus). The everolimus chemical name is 40-O-(2-hydroxyethyl)-rapamycin and the chemical structure is shown in Figure 1-1 below.

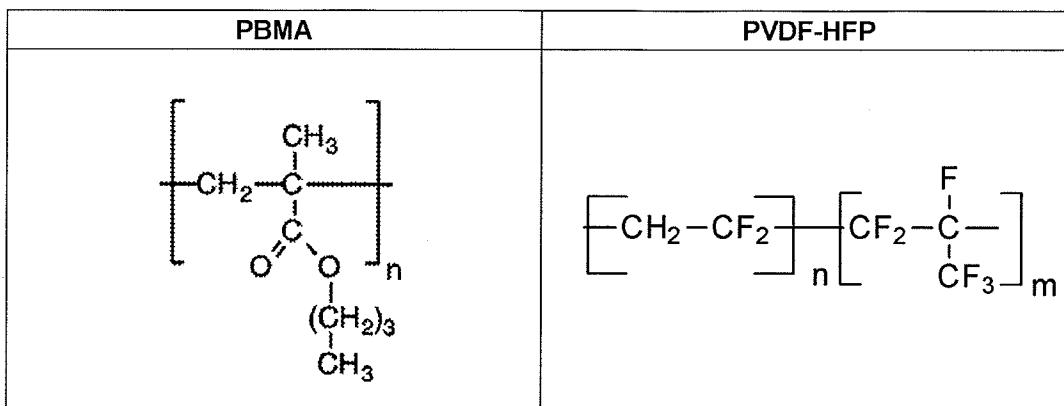
**Figure 1-1: Everolimus Chemical Structure**



### 1.2.2. Inactive Ingredients – Non-erodible Polymer

The PROMUS stent contains inactive ingredients including poly n-butyl methacrylate (PBMA), a polymer that adheres to the stent and drug coating, and PVDF-HFP, which is comprised of vinylidene fluoride and hexafluoropropylene monomers as the drug matrix layer containing everolimus. PBMA is a homopolymer with a molecular weight (Mw) of 264,000 to 376,000 dalton. PVDF-HFP is a non-erodible semi-crystalline random copolymer with a molecular weight (Mw) of 254,000 to 293,000 dalton. The drug matrix copolymer is mixed with everolimus (83%/17% w/w polymer/everolimus ratio) and applied to the entire PBMA coated stent surface. The drug load is 100 µg/cm<sup>2</sup> for all product sizes. No topcoat layer is used. The polymer chemical structures are shown in Figure 1-2 below.

Figure 1-2: Non-erodible Polymer Chemical Structures



### 1.2.3 Product Matrix and Everolimus Content

**Table 1-3: PROMUS EECSS Product Matrix and Everolimus Content**

Model Number (RX)	Model Number (OTW)	Nominal Expanded Stent Diameter (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Everolimus Content ( $\mu$ g)
1009539-08B	1009545-08B	2.5	8	37
1009540-08B	1009546-08B	2.75	8	37
1009541-08B	1009547-08B	3.0	8	37
1009542-08B	1009548-08B	3.5	8	53
1009543-08B	1009549-08B	4.0	8	53
1009539-12B	1009545-12B	2.5	12	56
1009540-12B	1009546-12B	2.75	12	56
1009541-12B	1009547-12B	3.0	12	56
1009542-12B	1009548-12B	3.5	12	75
1009543-12B	1009549-12B	4.0	12	75
1009539-15B	1009545-15B	2.5	15	75
1009540-15B	1009546-15B	2.75	15	75
1009541-15B	1009547-15B	3.0	15	75
1009542-15B	1009548-15B	3.5	15	98
1009543-15B	1009549-15B	4.0	15	98
1009539-18B	1009545-18B	2.5	18	88
1009540-18B	1009546-18B	2.75	18	88
1009541-18B	1009547-18B	3.0	18	88
1009542-18B	1009548-18B	3.5	18	113
1009543-18B	1009549-18B	4.0	18	113
1009539-23B	1009545-23B	2.5	23	113
1009540-23B	1009546-23B	2.75	23	113
1009541-23B	1009547-23B	3.0	23	113
1009542-23B	1009548-23B	3.5	23	151
1009543-23B	1009549-23B	4.0	23	151
1009539-28B	1009545-28B	2.5	28	132
1009540-28B	1009546-28B	2.75	28	132
1009541-28B	1009547-28B	3.0	28	132
1009542-28B	1009548-28B	3.5	28	181
1009543-28B	1009549-28B	4.0	28	181

## 2.0 INDICATIONS

The PROMUS Everolimus-Eluting Coronary Stent System (PROMUS stent) is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length  $\leq$  28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.

## 3.0 CONTRAINDICATIONS

The PROMUS stent is contraindicated for use in patients:

- Who cannot receive antiplatelet and/or anti-coagulant therapy (see **Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen** for more information)
- With lesions that prevent complete angioplasty balloon inflation or proper placement of the stent or stent delivery system
- With hypersensitivity or contraindication to everolimus or structurally-related compounds, cobalt, chromium, nickel, tungsten, acrylic, and fluoropolymers

#### 4.0 WARNINGS

- Ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Judicious patient selection is necessary because device use has been associated with stent thrombosis, vascular complications, and/or bleeding events.
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy (see Section 5.2 for important information regarding antiplatelet therapy).

#### 5.0 PRECAUTIONS

##### 5.1 General Precautions

- Stent implantation should only be performed by physicians who have received appropriate training.
- Stent placement should be performed at hospitals where emergency coronary artery bypass graft surgery is accessible.
- Subsequent restenosis may require repeat dilatation of the arterial segment containing the stent. Long-term outcomes following repeat dilatation of the stent is presently unknown.
- Risks and benefits should be considered in patients with severe contrast agent allergies.
- Care should be taken to control the guiding catheter tip during stent delivery, deployment, and balloon withdrawal. Before withdrawing the stent delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.
- Stent thrombosis is a low-frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. Stent thrombosis is frequently associated with myocardial infarction (MI) or death. Data from the SPIRIT family of trials have been prospectively evaluated and adjudicated using both the protocol definition of stent thrombosis and the definition developed by the Academic Research Consortium (ARC), and demonstrate specific patterns of stent thrombosis that vary depending on the definition used (see **Section 8.2 Stent Thrombosis Definitions** and **Section 9.4 SPIRIT II and SPIRIT III Pooled Analysis**, for more information). In the SPIRIT family of trials analyzed to date, the differences in the incidence of stent thrombosis observed with the stent, used in the SPIRIT clinical trials, compared to the TAXUS stent have not been associated with an increased risk of cardiac death, MI, or all-cause mortality. Additional data from longer-term follow-up in the SPIRIT family of trials and analyses of DES-related stent thrombosis are expected and should be considered in making treatment decisions as data become available.
- When DES are used outside the specified Indications for Use, patient outcomes may differ from the results observed in the SPIRIT family of trials.
- Compared to use within the specified Indications for Use, the use of DES in patients and lesions outside of the labeled indications, including more tortuous anatomy, may have an increased risk of adverse events, including stent thrombosis, stent embolization, MI, or death.

- Orally administered everolimus combined with cyclosporine is associated with increased serum cholesterol and triglycerides levels.

## 5.2 Pre- and Post-Procedure Antiplatelet Regimen

- In SPIRIT FIRST clinical trial, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 3 months post-procedure (75 mg per day). In SPIRIT II and SPIRIT III clinical trials, clopidogrel bisulfate or ticlopidine hydrochloride was administered pre-procedure and for a minimum of 6 months post-procedure (75 mg per day). Aspirin was administered (a minimum of 75 mg per day) pre-procedure and continued for 1 to 5 years (depending on the study). Based on the case report forms from the SPIRIT II and III randomized clinical trials, approximately 92% of patients remained on dual antiplatelet therapy at 6 months and 62% at 1 year See Section 9.0 – Clinical Studies, for more specific information.
- The optimal duration of dual antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy. Data from several studies on sirolimus-eluting or paclitaxel-eluting stents suggest that a longer duration of clopidogrel than was recommended post-procedurally in DES pivotal trials may be beneficial. Current guidelines recommend that patients receive aspirin indefinitely and that clopidogrel therapy be extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines<sup>1,2</sup>).
- It is very important that the patient is compliant with the post-procedural antiplatelet therapy recommendations. Early discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, MI, or death. Prior to percutaneous coronary intervention (PCI), if the patient is required to undergo a surgical or dental procedure that might require early discontinuation of antiplatelet therapy, the interventionalist and patient should carefully consider whether a DES and its associated recommended antiplatelet therapy is the appropriate PCI treatment of choice. Following PCI, should a surgical or dental procedure be recommended that requires suspension of antiplatelet therapy, the risks and benefits of the procedure should be weighed against the possible risks associated with early discontinuation of antiplatelet therapy. Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physicians, the antiplatelet therapy should be restarted as soon as possible.

## 5.3 Multiple Stent Use

A patient's exposure to drug and polymer is proportional to the number and total length of implanted stents. In the SPIRIT II and III clinical trials, treatment was limited to 36 mm of total stent length in up to two lesions in different epicardial vessels. Use of more than two stents to treat lesions longer than 28 mm has not been evaluated and may increase patient complication risks. Studies evaluating the effects of higher drug doses have not been conducted.

Effects of multiple stenting using PROMUS stents combined with other drug-eluting stents are also unknown. When multiple drug-eluting stents are required, use only PROMUS stents in order to avoid potential interactions with other drug-eluting or coated stents.

<sup>1</sup> Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121.

<sup>2</sup> King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209.

In addition, only stents composed of similar materials should be implanted in consecutive stent to stent contact to avoid corrosion potential between unrelated materials. Although *in vitro* tests combining L-605 CoCr alloy with 316 L stainless steel did not increase corrosion potential, these studies have not been conducted *in vivo*.

#### **5.4 Brachytherapy**

PROMUS stent safety and effectiveness has not been evaluated in patients with prior target lesion or in-stent restenosis-related brachytherapy.

#### **5.5 Use in Conjunction with Other Procedures**

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with PROMUS stent implantation have not been established.

#### **5.6 Use in Special Populations**

##### **5.6.1 Pregnancy**

Pregnancy Category C. See Section 6.5 – Drug Information, Pregnancy. The PROMUS stent has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effective contraception should be initiated before implanting a PROMUS stent and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

##### **5.6.2 Lactation**

See Section 6.6 – Drug Information, Lactation. A decision should be made whether to discontinue nursing prior to stent implantation considering the importance of the stent to the mother.

##### **5.6.3 Gender**

No safety- or effectiveness-related gender differences were observed in the individual SPIRIT clinical trials.

##### **5.6.4 Ethnicity**

Insufficient SPIRIT clinical trial subject numbers prevent ethnicity-related analyses on safety and effectiveness.

### **5.6.5 Pediatric Use**

Safety and effectiveness of the PROMUS stent in pediatric subjects have not been established.

### **5.6.6 Geriatric Use**

SPIRIT clinical studies did not suggest that patients age 65 years and over differed with regard to safety and effectiveness compared to younger patients.

## **5.7 Lesion/Vessel Characteristics**

Safety and effectiveness of the PROMUS stent have not been established for subject populations with the following clinical settings:

- Unresolved vessel thrombus at the lesion site
- Coronary artery reference vessel diameters < 2.5 mm or > 4.25 mm
- Lesion lengths > 28 mm
- Lesions located in saphenous vein grafts
- Lesions located in unprotected left main coronary artery, ostial lesions, chronic total occlusions, lesions located at a bifurcation
- Previously stented lesions
- Diffuse disease or poor flow (TIMI < 1) distal to the identified lesions
- Excessive tortuosity proximal to or within the lesion
- Recent acute myocardial infarction (AMI) or evidence of thrombus in the target vessel
- Moderate or severe lesion calcification
- Multivessel disease
- In-stent restenosis
- Patients with longer than 24 months follow-up.

## **5.8 Drug Interactions**

See Section 6.3 – Drug Information, Interactions with Drugs or Other Substances.

Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both cytochrome P4503A4 (CYP3A4) and P-glycoprotein. Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the PROMUS stent because of limited systemic exposure to everolimus eluted from the stent used in SPIRIT clinical trials (see Section 6.2 Pharmacokinetics). Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the PROMUS stent in a patient taking a drug with known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received a PROMUS Stent.

### **5.9 Immune Suppression Potential**

Everolimus, the PROMUS stent active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the SPIRIT clinical trials. However, for patients who receive several PROMUS stents simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

### **5.10 Lipid Elevation Potential**

Oral everolimus use in renal transplant patients was associated with increased serum cholesterol and triglycerides that in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the PROMUS stent are expected to be significantly lower than concentrations usually obtained in transplant patients. Increased serum cholesterol and triglycerides were not observed in the SPIRIT family of clinical trials.

### **5.11 Magnetic Resonance Imaging (MRI)**

Non-clinical testing has demonstrated that the PROMUS stent, in single and in overlapped configurations up to 68 mm in length, is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 or 3 Tesla
- Spatial gradient field of 720 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 2.0 W/kg (normal operating mode) for 15 minutes of scanning or less

The PROMUS stent should not migrate in this MRI environment. Non-clinical testing at field strengths greater than 3 Tesla has not been performed to evaluate stent migration or heating. MRI at 1.5 or 3 Tesla may be performed immediately following the implantation of the PROMUS stent.

Stent heating was derived by relating the measured non-clinical, *in vitro* temperature rises in a GE Excite 3 Tesla scanner and in a GE 1.5 Tesla coil to the local specific absorption rates (SARs) in a digitized human heart model. The maximum whole body averaged SAR was determined by validated calculation. At overlapped lengths up to 68 mm, the PROMUS stent produced a non-clinical maximum local temperature rise of 3°C at a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for 15 minutes. These calculations do not take into consideration the cooling effects of blood flow.

The effects of MRI on overlapped stents greater than 68 mm in length or stents with fractured struts are unknown.

As demonstrated in non-clinical testing, an image artifact can be present when scanning the PROMUS stent. MR image quality may be compromised if the area of interest is in the exact same area, or relatively close to, the position of the PROMUS stent. Therefore, it may be necessary to optimize the MR imaging parameters for the presence of PROMUS stents.

## 5.12 Stent Handling

- **Each stent is for single use only.** Do not resterilize or reuse this device. Note the "use by" (expiration) date on the product label.
- **The foil pouch is not a sterile barrier.** The inner header bag (pouch) within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.
- **Do not remove the stent from the delivery system.** Removal may damage the stent and/or lead to stent embolization. These components are intended to perform together as a system.
- The delivery system should not be used in conjunction with other stents.
- Special care must be taken not to handle or disrupt the stent on the balloon especially during delivery system removal from packaging, placement over the guide wire and advancement through the rotating hemostatic valve adapter and guiding catheter hub.
- **Do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination, or stent dislodgement from the delivery balloon.
- Use only the appropriate balloon inflation media (see Section 13.3.3 – Operator's Instructions, Delivery System Preparation). Do not use air or any gaseous medium to inflate the balloon as this may cause uneven expansion and difficulty in stent deployment.

## 5.13 Stent Placement

### 5.13.1 Stent Preparation

- **Do not prepare or pre-inflate the delivery system prior to stent deployment other than as directed.** Use the balloon purging technique described in Section 13.3.3 – Operator's Instructions, Delivery System Preparation.
- **Do not induce negative pressure on the delivery system prior to placing the stent across the lesion.** This may cause dislodgement of the stent from the balloon.
- Use guiding catheters which have lumen sizes that are suitable to accommodate the stent delivery system (see Section 1.1 – Product Description, Device Component Description).

### 5.13.2 Stent Implantation

- The vessel should be pre-dilated with an appropriate sized balloon. Failure to do so may increase the difficulty of stent placement and cause procedural complications.
- Do not expand the stent if it is not properly positioned in the vessel (see Section 5.14 – Precautions, Stent System Removal).
- Implanting a stent may lead to vessel dissection and acute closure requiring additional intervention (CABG, further dilatation, placement of additional stents, or other).
- Although the safety and effectiveness of treating more than one vessel per coronary artery with PROMUS stents has not been established, if this is performed, place the stent in the distal lesion before the proximal lesion in order to minimize dislodgement risk incurred by traversing through deployed stents.
- Stent placement may compromise side branch patency.
- **Do not exceed Rated Burst Pressure (RBP) as indicated on product label.** See Table 14-1, Typical PROMUS EECSS Compliance. Balloon pressures should be monitored during inflation. Applying pressures higher than specified on the product label may result in a

ruptured balloon with possible arterial damage and dissection. The stent inner diameter should approximate 1.1 times the reference diameter of the vessel.

- An unexpanded stent may be retracted into the guiding catheter one time only. An unexpanded stent should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end of the guiding catheter should not be performed as the stent may be damaged when retracting the undeployed stent back into the guiding catheter.
- Should **any resistance** be felt at **any time** during coronary stent system withdrawal, the stent delivery system and guiding catheter should be **removed as a single unit** (see Section 5.14 – Precautions, Stent System Removal).
- Stent retrieval methods (i.e., using additional wires, snares, and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.
- Although the stent delivery system balloon is strong enough to expand the stent without rupture, a circumferential balloon tear distal to the stent and prior to complete stent expansion, could cause the balloon to become tethered to the stent, requiring surgical removal. In case of balloon rupture, it should be withdrawn and, if necessary, a new dilatation catheter exchanged over the guide wire to complete the expansion of the stent.
- Ensure the stented area covers the entire lesion/dissection site and that no gaps exist between stents.

#### **5.14 Stent System Removal**

Should **any resistance** be felt at **any time** during either lesion access or removing the delivery system post-stent implantation, the stent delivery system and the guiding catheter should be **removed as a single unit**.

**When removing the delivery system and guiding catheter as a single unit, the following steps should be executed under direct visualization using fluoroscopy:**

- Confirm complete balloon deflation. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position. In some cases it may be necessary to slightly retract the guiding catheter in order to prevent unplanned guiding catheter movement and subsequent vessel damage. In cases where unplanned guiding catheter movement has occurred, a coronary tree angiographic assessment should be undertaken to ensure that there is no damage to the coronary vasculature.
- DO NOT retract the delivery system into the guiding catheter.
- Position the proximal balloon marker just distal to guiding catheter tip.
- Advance the guide wire into the coronary anatomy as far distally as safely possible.
- Tighten the rotating hemostatic valve to secure the delivery system to the guiding catheter, and remove the guiding catheter and delivery system as a **single unit**.

Failure to follow these steps and/or applying excessive force to the delivery system can potentially result in loss or damage to the stent and/or delivery system components.

If it is necessary to retain guide wire position for subsequent artery/lesion access, leave the guide wire in place and remove all other system components.

Stent retrieval methods (i.e., additional wires, snares and/or forceps) may result in additional trauma to the coronary vasculature and/or the vascular access site. Complications may include, but are not limited to, bleeding, hematoma, or pseudoaneurysm.

### **5.15 Post-Procedure**

- When crossing a newly deployed stent with an intravascular ultrasound (IVUS) catheter, a coronary guide wire, a balloon catheter or delivery system, exercise care to avoid disrupting the stent placement, apposition, geometry, and/or coating.
- Antiplatelet therapy should be administered post-procedure (see Section 5.2 Pre- and Post-Procedure Antiplatelet Regimen and Section 9.0 Clinical Studies). Patients who require early discontinuation of antiplatelet therapy (e.g., secondary to active bleeding) should be monitored carefully for cardiac events. At the discretion of the patient's treating physician, the antiplatelet therapy should be restarted as soon as possible.
- If the patient requires imaging, see Section 5.11 – Precautions, Magnetic Resonance Imaging (MRI).

## **6.0 DRUG INFORMATION**

### **6.1 Mechanism of Action**

The mechanism by which the PROMUS Stent inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FRAP (FKBP-12 Rapamycin Associated Protein), also known as mTOR (mammalian Target Of Rapamycin), leading to inhibition of cell metabolism, growth and proliferation by arresting the cell cycle at the late G1 stage.

### **6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent**

The PROMUS Everolimus-Eluting Coronary Stent System is a private label XIENCE V Everolimus Eluting Coronary Stent System manufactured by Abbott and distributed by Boston Scientific Corporation. Everolimus pharmacokinetics (PK) when eluted from the XIENCE V stent used in the SPIRIT clinical trials post-implantation has been evaluated in three different substudies in three different geographies. The SPIRIT III clinical trial design includes a pharmacokinetic substudy in the US randomized arm and a pharmacokinetic substudy in the Japanese non-randomized arm. The third PK substudy was conducted as part of the SPIRIT II clinical trial at sites in Europe, India, and New Zealand. Whole blood everolimus PK parameters determined from subjects receiving the XIENCE V stent are provided in Table 6-1.

**Table 6-1: Whole Blood Everolimus Pharmacokinetic Parameters in Patients Following XIENCE V Stent Implantation**

<b>SPIRIT III RCT and 4.0 Arm</b>							
	Dose ( $\mu\text{g}$ )	$t_{\max}$ (h)	$C_{\max}$ (ng/mL)	$t_{1/2}$ (h) <sup>a</sup>	$AUC_{0-t}^{\text{a}}$ (ng.h/mL)	$AUC_{0-\infty}^{\text{a}}$ (ng.h/mL)	CL (L/h) <sup>a</sup>
		median (range)	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD
2.5-3.0 x 18 mm (n=3 <sup>b</sup> )	88 $\mu\text{g}$	0.050 (0.50-1.88)	0.3867 $\pm$ 0.09866		5.31 $\pm$ 4.114		
3.5-4.0 x 28 mm (n=6 <sup>c</sup> )	181 $\mu\text{g}$	0.50 (0.07-1.00)	1.175 $\pm$ 0.6817	79.08 $\pm$ 57.24	23.73 $\pm$ 13.63	44.00 $\pm$ 28.67	5.130 $\pm$ 2.114
<b>SPIRIT III Japanese Arm</b>							
	Dose ( $\mu\text{g}$ )	$t_{\max}$ (h)	$C_{\max}$ (ng/mL)	$t_{1/2}$ (h) <sup>a</sup>	$AUC_{0-t}$ (ng.h/mL)	$AUC_{0-\infty}^{\text{a}}$ (ng.h/mL)	CL (L/h)
		median (range)	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD
2.5-3.0 x 18 mm (n=6)	88 $\mu\text{g}$	1.00 (0.50-1.02)	0.5017 $\pm$ 0.1398	45.22 $\pm$ 35.08	5.049 $\pm$ 2.138	12.98 $\pm$ 7.078	9.286 $\pm$ 6.069
3.5-4.0 x 18 mm (n=4 <sup>d</sup> )	113 $\mu\text{g}$	0.51 (0.50-0.53)	0.6500 $\pm$ 0.08756	53.57 $\pm$ 19.34	11.02 $\pm$ 4.002	19.97 $\pm$ 7.890	6.471 $\pm$ 2.807
<b>SPIRIT II Clinical Trial</b>							
	Dose ( $\mu\text{g}$ )	$t_{\max}$ (h)	$C_{\max}$ (ng/mL)	$t_{1/2}$ (h) <sup>a</sup>	$AUC_{last}$ (ng.h/mL)	$AUC_{0-\infty}^{\text{a}}$ (ng.h/mL)	CL (L/h) <sup>a</sup>
		median (range)	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD
2.5-3.0 x 18 mm (n=13)	88 $\mu\text{g}$	0.50 (0.13-2.17)	0.4369 $\pm$ 0.1507	54.08 $\pm$ 35.78	8.255 $\pm$ 5.863	19.60 $\pm$ 15.30	8.066 $\pm$ 6.443
3.5-4.0 x 18 mm (n=4 <sup>e</sup> )	113 $\mu\text{g}$	0.50 (0.50-0.50)	0.5850 $\pm$ 0.2630	47.60 $\pm$ 62.13	42.54 $\pm$ 58.83	22.79 $\pm$ 31.47	16.96 $\pm$ 13.07
3.5-4.0 x 28 mm (n=4)	181 $\mu\text{g}$	0.46 (0.17-1.00)	0.7925 $\pm$ 0.1406	103.4 $\pm$ 64.17	28.07 $\pm$ 13.18	52.71 $\pm$ 27.40	5.332 $\pm$ 5.048

<sup>a</sup> Accurate determination not possible due to rapid disappearance of everolimus from the blood

<sup>b</sup> n= 5 for  $t_{1/2}$  and CL.

<sup>c</sup> n= 3 for  $t_{1/2}$  and CL.

$t_{\max}$ (h)= time to maximum concentration.

$C_{\max}$ = maximum observed blood concentration.

$t_{1/2}$  (h)= terminal phase half-life.

$AUC_{0-t}$  or  $AUC_{last}$  = the area beneath the blood concentration versus time curve: time zero to the final quantifiable concentration

$AUC_{(0-\infty)}$  = the area beneath the blood concentration versus time curve: time zero to the extrapolated infinite time

CL= total blood clearance.

In all subjects, the maximum time to everolimus disappearance was 168 hours; however, 1 subject in the SPIRIT II clinical trial had detectable levels at 30 days. In all 3 studies, the  $C_{\max}$  value never reached the minimum therapeutic value of 3.0 ng/mL necessary for effective systemic administration to prevent organ rejection. The PK parameters representing elimination;  $t_{1/2}$ ,  $AUC_{0-t}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ , and CL could also not be determined accurately due to rapid everolimus disappearance from blood. These types of results have been seen with other drug-eluting stents.

Everolimus disappearance from circulation following XIENCE V stent implantation should further limit systemic exposure and adverse events associated with long-term systemic administration at therapeutic levels. Despite limited systemic exposure to everolimus, local arterial delivery has been demonstrated in pre-clinical studies.

### **6.3 Interactions with Drugs or Other Substances**

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver and is a substrate for the countertransporter P-glycoprotein. Therefore, absorption and subsequent elimination of everolimus may be influenced by drugs that also affect this pathway. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the PROMUS stent because of limited systemic exposure to everolimus eluted from the stent used in the SPIRIT clinical trials, (see Section 6.2 Pharmacokinetics). However, consideration should be given to the potential for both systemic and local drug interactions in the vessel wall when deciding to place the PROMUS stent in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with the drugs/foods<sup>3</sup> listed below. Medications that are strong inhibitors of CYP3A4 might reduce everolimus metabolism *in vivo*. Hence, co-administration of strong inhibitors of CYP3A4 may increase the blood concentrations of everolimus.

- CYP3A4 isozyme inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, erythromycin, clarithromycin, fluconazole, calcium channel blockers)
- Inducers of CYP3A4 isozyme (rifampin, rifabutin, carbamazepin, phenobarbital, phenytoin)
- Antibiotics (ciprofloxacin, ofloxacin)
- Glucocorticoids
- HMGCoA reductase inhibitors (simvastatin, lovastatin)
- Digoxin
- Cisapride (theoretical potential interaction)
- Sildenafil (Viagra®) (theoretical potential interaction)
- Antihistaminics (terfenadine, astemizole)
- Grapefruit juice

### **6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity**

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of PROMUS stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group (PROMUS stent). The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group. Based on the results of this study, the PROMUS stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

Genotoxicity studies were conducted on the PROMUS stent in mammalian cells and bacteria. These studies included gene mutations in bacteria (Ames Test), gene mutations in mammalian cells (chromosomal aberration), test for clastogenicity in mammalian cells, and mammalian erythrocyte micronucleus test. Based on the results of these studies, the PROMUS stent is not genotoxic.

<sup>3</sup> Certican® Investigator's Brochure. Novartis Pharmaceutical Corporation

In addition, a reproductive toxicity (teratology) study was conducted to demonstrate that implantation of PROMUS stents in female Sprague-Dawley rats does not affect their fertility or reproductive capability and shows a lack of any reproductive toxicity on their offspring. The PROMUS stent did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article (PROMUS stent) and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of in utero mortality. Additionally, the PROMUS stent did not cause any reproductive toxicity in the offspring in this study.

## 6.5 Pregnancy

Pregnancy Category C: There are no adequate everolimus or PROMUS stent related studies in pregnant women. Effects of the PROMUS stent on prenatal and postnatal rat development were no different than the controls. When administered at oral doses of 0.1 mg/kg or above, everolimus showed effects on prenatal and postnatal rat development limited to slight body weight changes and fetal survival without any specific toxic potential.

Effective contraception should be initiated before implanting a PROMUS stent and continued for one year post-implantation. The PROMUS stent should be used in pregnant women only if potential benefits justify potential risks.

Safety of the PROMUS stent has not been evaluated in males intending to father children.

## 6.6 Lactation

It is unknown whether everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to PROMUS stent implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

## 7.0 OVERVIEW OF CLINICAL STUDIES

The PROMUS Everolimus-Eluting Coronary Stent System is a private label XIENCE V Everolimus Eluting Coronary Stent System manufactured by Abbott and distributed by Boston Scientific Corporation. Principal XIENCE V safety and effectiveness information is derived from the SPIRIT III clinical trial and is supported by the SPIRIT FIRST and SPIRIT II clinical trials. These studies evaluated XIENCE V EECSS performance in subjects with symptomatic ischemic disease due to *de novo* lesions in native coronary arteries. Major study characteristics are summarized below and listed in Table 7-1.

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS<sup>2</sup>™ Paclitaxel Eluting Coronary Stent System (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consisted of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Enrollment is complete in the RCT and the Japan arm.

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EL2064613 (6/30/08)

The SPIRIT III RCT was a prospective, randomized (2:1; XIENCE V:TAXUS), active-controlled, single-blinded, multi-center, clinical trial in the US designed to evaluate the safety and efficacy of the XIENCE V stent in the treatment of up to two *de novo* lesions  $\leq$  28 mm in length in native coronary arteries with RVD  $\geq$  2.5 mm to  $\leq$  3.75 mm. The RCT study was designed to enroll 1,002 subjects at up to 80 sites in the US. The primary endpoint in the RCT was in-segment late loss at 240 days, and the co-primary endpoint was ischemia-driven target vessel failure (TVF, defined as the composite of cardiac death, MI, or clinically-driven TVR) at 270 days. Other secondary endpoints included clinical outcomes of all the subjects (30, 180, 270 days and annually from 1 to 5 years), as well as angiographic results and intravascular ultrasound (IVUS) results at 240 days. Follow-up through 1 year is currently available, and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III 4.0 mm arm was a prospective, multi-center, single-arm registry designed to evaluate the XIENCE V stent in the treatment of up to two *de novo* lesions  $\leq$  28 mm in length in native coronary arteries with RVD  $>$  3.75 mm to  $\leq$  4.25 mm. This study was designed to enroll up to 80 subjects at up to 80 sites in the US. Enrolled subjects were scheduled for clinical follow-up at 30, 180, 240, and 270 days and annually from 1 to 5 years, with angiographic follow-up at 240 days. The primary endpoint was in-segment late loss at 240 days compared to the TAXUS arm from the SPIRIT III RCT. Follow-up through 1 year is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT III clinical trial included a pharmacokinetic substudy in a subset derived from the RCT<sup>4</sup> and Japan non-randomized arm. Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan).

The SPIRIT II clinical trial was a randomized, single-blind, active-control, multi-center clinical evaluation. Subject eligibility criteria were similar to the SPIRIT III clinical trial and enrollment duration overlapped between studies. In this study, 300 subjects (3:1 randomization XIENCE V: TAXUS) were enrolled at 28 sites outside the United States. The primary endpoint was in-stent late loss at 6 months. Secondary endpoints included clinical outcomes at 30, 180, 270 days and annually from 1 to 5 years; angiographic results at 180 days and 2 years; and IVUS results at 180 days and 2 years. Clinical follow-up through 2 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

The SPIRIT FIRST clinical trial was a randomized, single-blind, controlled, multi-center first-in-man study. This trial was the first human study to evaluate the XIENCE V stent safety and performance. Sixty subjects [XIENCE V stent (n=28) and MULTI-LINK VISION bare metal control stent (n=32)] were enrolled at 9 sites in Europe. The primary endpoint was in-stent late loss at 6 months on the per-treatment evaluable population, and the major secondary endpoint was the percent in-stent volume obstruction (% VO) at 6 months based on IVUS analysis of the per-treatment evaluable population. Follow-up through 3 years is currently available and yearly follow-up for clinical parameters through 5 years is ongoing.

Table 7-1 summarizes the clinical trial designs for the SPIRIT family of trials.

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<sup>4</sup> Includes one subject from the 4.0 mm non-randomized arm.

**Table 7-1: XIENCE V SPIRIT Clinical Trial Designs**

	SPIRIT III clinical trial		SPIRIT II clinical trial		SPIRIT FIRST clinical trial	
	RCT	Registries	Multi-center	Randomized	Multi-center	Randomized
<b>Study Type/Design</b>	<ul style="list-style-type: none"> <li>• Multi-center</li> <li>• Randomized</li> <li>• Single-blinded</li> <li>• Active-Control</li> </ul>	<ul style="list-style-type: none"> <li>• Multi-center</li> <li>• Single-arm</li> <li>• Open-label</li> </ul>	<ul style="list-style-type: none"> <li>• Single-blinded</li> <li>• Active-Control</li> </ul>	<ul style="list-style-type: none"> <li>• Multi-center</li> <li>• Randomized</li> <li>• Single-blinded</li> <li>• Control</li> </ul>	<ul style="list-style-type: none"> <li>• Multi-center</li> <li>• Randomized</li> <li>• Single-blinded</li> </ul>	<ul style="list-style-type: none"> <li>• Single-blinded</li> </ul>
<b>Number of Subjects Enrolled</b>	Total: 1,002 XIENCE V: 668 TAXUS Control: 334	Total: 168 4.0 mm: 80 Japan: 88*	Total: 300 XIENCE V: 225 VISION Control: 30	Total: 60 XIENCE V: 30 VISION Control: 30		
<b>Treatment</b>	Up to two de novo lesions in different epicardial vessels	Up to two de novo lesions in different epicardial vessels	Up to two de novo lesions in different epicardial vessels	Up to two de novo lesions in different epicardial vessels	Single de novo lesion	
<b>Lesion Size</b>	RVD: $\geq 2.5 \leq 3.75$ mm Length: $\leq 28$ mm	4.0 mm RVD: $\geq 3.75 \leq 4.25$ mm Length: $\leq 28$ mm	4.0 mm RVD: $\geq 2.5 \leq 4.25$ mm Length: $\leq 28$ mm	RVD: $\geq 2.5 \leq 4.25$ mm Length: $\leq 28$ mm	RVD: 3 mm Length: $\leq 12$ mm	
<b>Stent Sizes (XIENCE V)</b>	Diameter: 2.5, 3.0, 3.5 mm Length: 8, 18, 28 mm	4.0 mm Diameter: 4.0 mm Length: 8, 18, 28 mm	4.0 mm Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 2.5, 3.0, 3.5, 4.0 mm Length: 8, 18, 28 mm	Diameter: 3.0 mm Length: 18 mm	
<b>Post-procedure Antiplatelet Therapy</b>	Clopidogrel 6 months minimum (or ticlopidine per site standard), Aspirin 5 years	4.0 mm: same as RCT Japan: Ticlopidine 3 months, Aspirin 5 years	Clopidogrel 6 months minimum (or ticlopidine per site standard), Aspirin 1 year	In-stent late loss at 240-days	In-stent late loss at 180-days	
<b>Primary Endpoint</b>	In-segment late loss at 240-days	None	None	None	None	In-stent late loss at 180-days
<b>Co-Primary Endpoint</b>	TVF at 270-days	30, 180, 240, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	30, 180, 270 days, 1 to 5 years	
<b>Clinical Follow-up</b>	240 days (N=564)	240 days (All registry)	180-day (all), 2-years (N=152)	180-day, 2-years (N=152)	180-days, 1-year (all)	
<b>Angiographic Follow-up</b>	240 days (N=240)	240 days (Japan only)	180-day, 2-years (N=152)	180-day/s, 1-year (all)	180-day/s, 1-year (all)	
<b>IVUS Follow-up</b>	US: Minimum 15 subjects with single lesion, maximum 20 with dual lesions Japan: Minimum 10 subjects with single lesion, maximum 20 with dual lesions	Minimum 15 subjects with single lesion, maximum 20 with dual lesions	Minimum 15 subjects with single lesion, maximum 20 with dual lesions	None	None	
<b>PK Study</b>	One year reported; 2, 3, 4 and 5 years planned	One and 2 years reported; 3, 4 and 5 years planned	One and 2 years reported; 3, 4 and 5 years planned	One, 2, and 3 years reported and 5 years planned	One, 2, and 3 years reported and 5 years planned	
<b>Status</b>						

\*Only pharmacokinetic substudy results included (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent).

## 8.0 ADVERSE EVENTS

### 8.1 Observed Adverse Events

Principal adverse event information is derived from SPIRIT III, SPIRIT II and SPIRIT FIRST clinical trials and is shown in Table 8.1-1 and 8.1-2. Within these tables, the Intent-to-Treat population includes all subjects randomized, while the Per-Treatment Evaluable population includes only those subjects who received a study device at the target lesion with no major procedure protocol deviations except deviations relating to the treatment arm, for whom follow-up data are available. See also Section 8.3 – Adverse Events, Potential Adverse Events. See Section 9.0 – Clinical Studies for more complete study design descriptions and results.

**Table 8.1-1: SPIRIT III, II and FIRST:  
Principal Adverse Events From Post-Procedure to 1 Year**

	SPIRIT III		SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)
<b>In Hospital</b>						
TVF <sup>1</sup>	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)
MACE <sup>2</sup>	0.9% (6/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	3.7% (1/27)
All Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)
Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)
Non-Cardiac Death	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)
MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)
QMI	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)
NQMI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)
Cardiac Death or MI	0.7% (5/669)	2.4% (8/330)	4.3% (3/69)	0.9% (2/223)	2.6% (2/77)	0.0% (0/27)
Ischemia-Driven Revascularization	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)
Ischemia-Driven TLR	0.1% (1/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	3.7% (1/27)
Ischemia-Driven Non-TLR TVR	0.0% (0/669)	0.0% (0/330)	0.0% (0/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)
Stent Thrombosis <sup>3</sup> (Per Protocol)	0.3% (2/669)	0.0% (0/330)	1.4% (1/69)	0.0% (0/223)	0.0% (0/77)	0.0% (0/27)
<b>9 Months<sup>4</sup></b>						
TVF <sup>1</sup>	7.6% (50/657)	9.7% (31/320)	5.9% (4/68)	4.5% (10/220)	6.5% (5/77)	7.7% (2/26)
MACE <sup>2</sup>	5.0% (33/657)	8.8% (28/320)	5.9% (4/68)	2.7% (6/220)	6.5% (5/77)	7.7% (2/26)
All Death	1.1% (7/658)	0.9% (3/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)
Cardiac Death	0.6% (4/658)	0.6% (2/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)

EL2064613 (7/2/08)

Page 20 of 60

Printed on : 10/08/2009

A3472

	SPIRIT III			SPIRIT II		SPIRIT FIRST	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.3% (15/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
QMI	0.2% (1/657)	0.0% (0/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.1% (14/657)	3.1% (10/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Ischemia-Driven Revascularization	5.3% (35/657)	6.6% (21/320)	1.5% (1/68)	3.6% (8/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	1.5% (1/68)	1.8% (4/220)	3.9% (3/77)	3.8% (1/26)	21.4% (6/28)
Ischemia-Driven TVR, non TLR TVR	2.9% (19/657)	4.1% (13/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis <sup>3</sup>							
Protocol	0.6% (4/654)	0.0% (0/319)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
1 Year <sup>4</sup>							
TVF <sup>1</sup>	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	4.5% (10/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
MACE <sup>2</sup>	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	2.7% (6/220)	9.1% (7/77)	15.4% (4/26)	21.4% (6/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	0.9% (2/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.0% (0/222)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	0.9% (2/222)	0.0% (0/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/220)	0.0% (0/77)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	0.9% (2/220)	3.9% (3/77)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	0.9% (2/220)	3.9% (3/77)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	3.6% (8/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	1.8% (4/220)	6.5% (5/77)	7.7% (2/26)	21.4% (6/28)
Ischemia-Driven non-TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	1.8% (4/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Stent Thrombosis <sup>3</sup>							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	0.5% (1/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.0% (0/220)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)

EL2064613 (7/2/08)

Page 21 of 60

Printed on : 10/08/2009

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	SPIRIT III		SPIRIT II		SPIRIT FIRST		
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)

**Notes:**

- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s) / lesion(s) for subjects with two target vessels/lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- SPIRIT II and III based on Intent to Treat Population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population [a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm (randomized versus actually received)].
- Revascularization includes TLR and Non-TLR TVR.
- Q wave MI for all SPIRIT Trials is defined as the development of new pathological Q wave on the ECG.
- Non Q wave MI for SPIRIT III is defined as the elevation of CK levels to greater than or equal to 2 times the upper limit of normal with elevated CKMB in the absence of new pathological Q waves.
- Non Q wave MI for SPIRIT II is defined as a typical rise and fall of CKMB with at least one of the following: Ischemia symptoms, ECG changes indicative of ischemia (ST segment elevation or depression), or coronary artery intervention.
  - o If non procedural/spontaneous MI, CKMB is greater than or equal to 2 times upper limit of normal.
  - o If post PCI, CKMB is greater than or equal to 3 times upper limit of normal.
  - o If post CABG, CKMB is greater than or equal to 5 times upper limit of normal.
- Non Q wave MI for SPIRIT FIRST is defined (WHO definition) as the elevation of post procedure CK levels to greater than or equal to 2 times the upper normal limit with elevated CKMB in the absence of new pathological Q waves.
- Non Q wave MI for SPIRIT FIRST is defined (ESC/ACC definition) as for non procedural, CKMB elevation greater than or equal to 2 times the upper normal limit, for post PCI, CKMB elevation greater than or equal to three times the upper normal limit, and for post CBAG, CKMB elevation greater than or equal to five times the upper normal limit.

<sup>1</sup> TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.

<sup>2</sup> MACE includes cardiac death, MI and ischemia-driven TLR.

<sup>3</sup> See Section 8.2 – Stent Thrombosis Definitions.

<sup>4</sup>SPIRIT III and SPIRIT FIRST includes 14 day window. SPIRIT III includes 9 month events identified at the 1 year follow-up.

<sup>5</sup>SPIRIT III and SPIRIT FIRST includes 28 day window.

**Table 8.1-2: SPIRIT III, II and FIRST:  
Principal Adverse Events from Latest Follow-up**

	SPIRIT III 1 Year <sup>4</sup>			SPIRIT II 2 Year <sup>4</sup>		SPIRIT FIRST 3 Year <sup>4</sup>	
	XIENCE V (N=669)	TAXUS (N=333)	XIENCE V 4.0 mm Arm (N=69)	XIENCE V (N=223)	TAXUS (N=77)	XIENCE V (N=27)	VISION (N=29)
TVF <sup>1</sup>	8.6% (56/653)	11.3% (36/320)	5.9% (4/68)	10.0% (21/211)	12.3% (9/73)	15.4% (4/26)	32.1% (9/28)
MACE <sup>2</sup>	6.0% (39/653)	10.3% (33/320)	5.9% (4/68)	6.6% (14/211)	11.0% (8/73)	15.4% (4/26)	25.0% (7/28)
All Death	1.2% (8/655)	1.2% (4/321)	1.5% (1/68)	3.7% (8/218)	6.5% (5/77)	0.0% (0/26)	0.0% (0/28)
Cardiac Death	0.8% (5/655)	0.9% (3/321)	1.5% (1/68)	0.5% (1/218)	1.3% (1/77)	0.0% (0/26)	0.0% (0/28)
Non-Cardiac Death	0.5% (3/655)	0.3% (1/321)	0.0% (0/68)	3.2% (7/218)	5.2% (4/77)	0.0% (0/26)	0.0% (0/28)
MI	2.8% (18/653)	4.1% (13/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
QMI	0.3% (2/653)	0.3% (1/320)	0.0% (0/68)	0.0% (0/211)	0.0% (0/73)	3.8% (1/26)	0.0% (0/28)
NQMI	2.5% (16/653)	3.8% (12/320)	4.4% (3/68)	2.8% (6/211)	5.5% (4/73)	3.8% (1/26)	0.0% (0/28)
Cardiac Death or MI	3.4% (22/653)	4.7% (15/320)	5.9% (4/68)	3.3% (7/211)	5.5% (4/73)	7.7% (2/26)	0.0% (0/28)
Ischemia-Driven Revascularization	6.1% (40/653)	7.5% (24/320)	1.5% (1/68)	7.1% (15/211)	9.6% (7/73)	7.7% (2/26)	32.1% (9/28)
Ischemia-Driven TLR	3.4% (22/653)	5.6% (18/320)	1.5% (1/68)	3.8% (8/211)	6.8% (5/73)	7.7% (2/26)	25.0% (7/28)
Ischemia-Driven non-TLR TVR	3.1% (20/653)	4.4% (14/320)	0.0% (0/68)	3.8% (8/211)	4.1% (3/73)	0.0% (0/26)	10.7% (3/28)
Stent Thrombosis <sup>3</sup>							
Per Protocol	0.8% (5/647)	0.6% (2/317)	1.5% (1/67)	1.9% (4/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)
ARC (Definite+Probable)	1.1% (7/648)	0.6% (2/317)	0.0% (0/67)	0.9% (2/211)	1.4% (1/73)	0.0% (0/26)	0.0% (0/28)

Notes:

- In-hospital is defined as hospitalization less than or equal to 7 days post-index procedure.
- All counts presented in this table are subject counts. Subjects are counted only once for each event for each time period.
- This table includes revascularizations on any target vessel(s) / lesion(s) for subjects with two target vessels/lesions treated.
- One subject in the SPIRIT III, TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- SPIRIT II and III based on Intent to Treat Population (all subjects randomized, regardless of the treatment they actually received).
- SPIRIT FIRST based on per-treatment evaluable population [a subset of subjects in the full analysis set, who had no bailout and no major protocol deviations other than those relating to treatment arm (randomized versus actually received)].
- Revascularization includes TLR and Non-TLR TVR.

<sup>1</sup> TVF includes cardiac death, MI, ischemia-driven TLR and TVR, non-target lesion.

<sup>2</sup> MACE includes cardiac death, MI and ischemia-driven TLR.

<sup>3</sup> See Section 8.2 – Stent Thrombosis Definitions.

<sup>4</sup> SPIRIT III, SPIRIT II and SPIRIT FIRST includes 28 day window.

## 8.2 Stent Thrombosis Definitions

Protocol defined stent thrombosis (ST) was categorized as acute (< 1 day), subacute (1 - 30 days) and late (> 30 days) and was defined as any of the following<sup>5</sup>:

- Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (angiographic appearance of thrombus within or adjacent to a previously treated target lesion)
- In the absence of angiography, any unexplained death, or acute MI (ST segment elevation or new Q-wave)<sup>6</sup> in the distribution of the target lesion within 30 days

All stent thrombosis events were also classified using the ST definitions proposed by the Academic Research Consortium (ARC)<sup>7</sup>. This was performed by an independent event committee blinded to the treatment group of the individual subject. The committee categorized each incident of ST by timing and level of probability (definite, probable, possible), and relation to the original index procedure (primary, secondary after revascularization). These categories are defined as follows:

### Timing:

- Early ST: 0 to 30 days post stent implantation
- Late ST: 31 days to 1 year post stent implantation
- Very late ST: > 1 year post stent implantation

### Level of probability:

- Definite ST - considered to have occurred by either angiographic or pathologic confirmation
- Probable ST - considered to have occurred after intracoronary stenting in the following cases:
  1. Any unexplained death within the first 30 days.
  2. Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.
- Possible ST - considered to have occurred with any unexplained death following 30 days after the intracoronary stenting until the end of trial follow-up<sup>8</sup>

## 8.3 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with percutaneous coronary and treatment procedures including coronary stent use in native coronary arteries include, but are not limited to:

- Abrupt closure
- Access site pain, hematoma, or hemorrhage
- Acute myocardial infarction

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<sup>5</sup> For SPIRIT FIRST Stent Thrombosis is defined as total occlusion by angiography at the stent site with abrupt onset of symptoms, elevated biochemical markers, and ECG changes consistent with MI.

<sup>6</sup> Non-specific ST/T changes, and cardiac enzyme elevations do not suffice.

<sup>7</sup> Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circ* 2007;115:2344-51.

<sup>8</sup> All data within this Instructions for Use is presented as definite + probable only.

- Allergic reaction or hypersensitivity to contrast agent or cobalt, chromium, nickel, tungsten, acrylic and fluoropolymers; and drug reactions to antiplatelet drugs or contrast agent
- Aneurysm
- Arterial perforation and injury to the coronary artery
- Arterial rupture
- Arteriovenous fistula
- Arrhythmias, atrial and ventricular
- Bleeding complications, which may require transfusion
- Cardiac tamponade
- Coronary artery spasm
- Coronary or stent embolism
- Coronary or stent thrombosis
- Death
- Dissection of the coronary artery
- Distal emboli (air, tissue or thrombotic)
- Emergent or non-emergent coronary artery bypass graft surgery
- Fever
- Hypotension and/or hypertension
- Infection and pain at insertion site
- Injury to the coronary artery
- Ischemia (myocardial)
- Myocardial infarction (MI)
- Nausea and vomiting
- Palpitations
- Peripheral ischemia (due to vascular injury)
- Pseudoaneurysm
- Renal failure
- Restenosis of the stented segment of the artery
- Shock/pulmonary edema
- Stroke/cerebrovascular accident (CVA)
- Total occlusion of coronary artery
- Unstable or stable angina pectoris
- Vascular complications including at the entry site which may require vessel repair
- Vessel dissection

Adverse events associated with daily oral administration of everolimus to organ transplant patients include but are not limited to:

- Abdominal pain
- Acne
- Anemia
- Coagulopathy
- Diarrhea
- Edema
- Hemolysis
- Hypercholesterolemia
- Hyperlipidemia
- Hypertension

- Hypertriglyceridemia
- Hypogonadism male
- Infections: wound infection, urinary tract infection, pneumonia, pyelonephritis, sepsis and other viral, bacterial and fungal infections
- Leukopenia
- Liver function test abnormality
- Lymphocele
- Myalgia
- Nausea
- Pain
- Rash
- Renal tubular necrosis
- Surgical wound complication
- Thrombocytopenia
- Venous thromboembolism
- Vomiting

There may be other potential adverse events that are unforeseen at this time.

## **9.0 SPIRIT FAMILY OF CLINICAL TRIALS**

### **9.1 SPIRIT III Pivotal Clinical Trial**

SPIRIT III, a pivotal clinical trial, was designed to demonstrate the non-inferiority of the XIENCE V stent to the TAXUS EXPRESS<sup>2™</sup> Paclitaxel Eluting Coronary Stent System (TAXUS stent) and was conducted in the United States (US) and Japan. The SPIRIT III clinical trial consists of a US randomized clinical trial (RCT), a non-randomized 4.0 mm diameter stent arm in the US, and a non-randomized arm in Japan, which included a pharmacokinetic substudy. Enrollment is complete in the RCT and the Japan arm.

The SPIRIT III clinical trial included a pharmacokinetic sub-study in a subject subset derived from the RCT<sup>9</sup> and Japan non-randomized arm (see Section 6.2 Pharmacokinetics of the XIENCE V Everolimus Eluting Coronary Stent). Eleven sites in the US and 9 sites in Japan participated in this substudy and have enrolled 34 subjects (17 subjects in the US and 17 subjects in Japan). Venous blood was drawn at regular intervals for pharmacokinetics analysis of total blood everolimus level at pre-determined sites.

#### **9.1.1 SPIRIT III Randomized Clinical Trial (RCT)**

**Primary Objective:** The objective of the SPIRIT III RCT was to demonstrate the non-inferiority in in-segment late loss at 240 days and target vessel failure at 270 days of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two *de novo* lesions  $\leq 28$  mm in length in native coronary arteries with a reference vessel diameter (RVD)  $\geq 2.5$  mm to  $\leq 3.75$  mm. If non-inferiority of in-segment late loss was demonstrated, it was pre-specified that testing for superiority could be conducted.

**Design:** The SPIRIT III RCT was a prospective, 2:1 (XIENCE V:TAXUS) randomized, active-controlled, single-blinded, parallel, multi-center non-inferiority evaluation of the XIENCE V stent

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<sup>9</sup> Includes one subject from the 4.0 mm non-randomized arm.

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compared to the TAXUS stent in the treatment of up to two *de novo* lesions  $\leq$  28 mm in length in native coronary arteries with RVD  $\geq$  2.5 mm to  $\leq$  3.75 mm. Given the available XIENCE V stent lengths of 8, 18 and 28 mm for this trial, in the XIENCE V arm, treatment of a target lesion  $>$  22 mm and  $\leq$  28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent. In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage. The RCT was designed to enroll 1,002 subjects at up to 80 sites in the United States.

All subjects had clinical follow-up at 30, 180, and 270 days and annually from 1 to 5 years. A pre-specified subgroup of 564 subjects had angiographic follow-up at 240 days. Of these 564, 240 subjects had IVUS at baseline and 240 days. Subjects that received a bailout stent also had IVUS at baseline and angiographic and IVUS follow-up at 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

**Demographics:** The mean age was 63.2 years for the XIENCE V arm and 62.8 for the TAXUS arm. The XIENCE V had 70.1% (469/669) males and the TAXUS arm had 65.7% (218/332) males. The XIENCE V arm had 32.3% (215/666) of subjects with prior cardiac interventions and the TAXUS arm had 29.5% (98/332). The XIENCE V arm had 29.6% (198/669) of subjects with a history of diabetes and the TAXUS arm had 27.9% (92/330). The XIENCE V had 15.4% (103/669) of subjects with a lesion treated in two vessels and TAXUS had 15.4% (51/332). The XIENCE V arm had 8.1% (54/669) of subjects with planned stent overlap. The XIENCE V arm had 8.6% (57/666) of subjects with a history of prior CABG while the TAXUS arm had 3.6% (12/332) ( $p = 0.0033$ ). The XIENCE V arm had 18.7% (123/657) of subjects with a history of unstable angina while the TAXUS arm had 25.1% (82/327) ( $p=0.0243$ ). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

**Results:** The results are presented in Table 9.1.1-1 (Primary endpoints), Table 9.1.1-2 (Clinical Results), Table 9.1.1-3 (Angiographic and IVUS Results), Figure 9.1.1-1 (TVF Free Survival) and Table 9.1.1-4 (ARC-Defined Stent Thrombosis). These analyses are based on the intent to treat population.

The co-primary endpoint of in-segment late loss at 240 days was met with measurements of  $0.14 \pm 0.41$  mm (301) for the XIENCE V arm and  $0.28 \pm 0.48$  mm (134) for the TAXUS arm ( $p < 0.0001$  for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-segment late loss at 240 days ( $p = 0.0037$ ).

The co-primary endpoint of ischemia-driven TVF through 284 days was met with rates of 7.6% (50/657) for the XIENCE V arm and 9.7% (31/320) for the TAXUS arm ( $p < 0.001$  for non-inferiority).

**Table 9.1.1-1: SPIRIT III RCT Primary Endpoints Results**

<b>Measurements</b>	<b>XIENCE V (N=669) (M=376)</b>	<b>TAXUS (N=333) (M=188)</b>	<b>Difference [95% CI]</b>	<b>Non-Inferiority P-Value</b>	<b>Superiority P-Value</b>
<b>8 Month<sup>1</sup> Late Loss, In-segment (mm)</b>	$0.14 \pm 0.41$ (301)	$0.28 \pm 0.48$ (134)	-0.14 [-0.23, -0.05] <sup>2</sup>	<0.0001 <sup>3</sup>	0.0037 <sup>4</sup>
<b>9 Month<sup>5</sup> Target Vessel Failure<sup>6</sup></b>	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%] <sup>2</sup>	<0.0001 <sup>7</sup>	Not Pre-specified

**Notes:**

- N is the total number of subjects; M is the total number of analysis lesions.
- One in SPIRIT III TAXUS arm subject did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

- Analysis results include 9 month events identified at the 1 year follow-up.

<sup>1</sup> 8 month time frame includes follow-up window (240 + 28 days).

<sup>2</sup> By normal approximation.

<sup>3</sup> One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.025 significance level.

<sup>4</sup> Two-sided p-value by superiority test using two-sample T-test, to be compared at a 0.05 significance level.

<sup>5</sup> 9 month time frame includes follow-up window (270 + 14 days).

<sup>6</sup> TVF is defined as hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

<sup>7</sup> One sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

Table 9.1.1-2: SPIRIT III RCT Clinical Results

	OUTCOMES AT 9 MONTHS			OUTCOMES AT 1 YEAR (latest available follow-up)		
	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI] <sup>1</sup>	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI] <sup>1</sup>
<b>COMPOSITE EFFICACY &amp; SAFETY</b>						
TVF <sup>2</sup>	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]	8.6% (56/653)	11.3% (36/320)	-2.67% [-6.75%, 1.40%]
MACE <sup>3</sup>	5.0% (33/657)	8.8% (28/320) <sup>7</sup>	-3.73% [-7.24%, -0.21%]	6.0% (39/653)	10.3% (33/320)	-4.34% [-8.14%, -0.54%]
<b>EFFICACY</b>						
Ischemia-Driven TLR	2.7% (18/657)	5.0% (16/320)	-2.26% [-4.95%, 0.43%]	3.4% (22/653)	5.6% (18/320)	-2.26% [-5.13%, 0.62%]
TLR, CABG	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.0% (0/320)	0.31% [Assump. not met]
TLR, PCI	2.6% (17/657)	5.0% (16/320)	-2.41% [-5.09%, 0.27%]	3.1% (20/653)	5.6% (18/320)	-2.56% [-5.41%, 0.29%]
Ischemia-Driven non-TLR TVR	2.9% (19/657)	4.1% (13/320)	-1.17% [-3.68%, 1.34%]	3.1% (20/653)	4.4% (14/320)	-1.31% [-3.91%, 1.29%]
non-TLR TVR, CABG	0.5% (3/657)	0.6% (2/320)	-0.17% [Assump. not met]	0.6% (4/653)	0.6% (2/320)	-0.01% [Assump. not met]
non-TLR TVR, PCI	2.4% (16/657)	3.4% (11/320)	-1.00% [-3.32%, 1.32%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
<b>SAFETY</b>						
All Death	1.1% (7/658)	0.9% (3/321)	0.13% [Assump. not met]	1.2% (8/655)	1.2% (4/321)	-0.02% [Assump. not met]
Cardiac Death	0.6% (4/658)	0.6% (2/321)	-0.02% [Assump. not met]	0.8% (5/655)	0.9% (3/321)	-0.17% [Assump. not met]
Non-Cardiac Death	0.5% (3/658)	0.3% (1/321)	0.14% [Assump. not met]	0.5% (3/655)	0.3% (1/321)	0.15% [Assump. not met]
MI	2.3% (15/657)	3.1% (10/320)	-0.84% [-3.06%, 1.38%]	2.8% (18/653)	4.1% (13/320)	-1.31% [-3.81%, 1.20%]
QMI	0.2% (1/657)	0.0% (0/320)	0.15% [Assump. not met]	0.3% (2/653)	0.3% (1/320)	-0.01% [Assump. not met]
NQMI	2.1% (14/657)	3.1% (10/320)	-0.99% [-3.20%, 1.21%]	2.5% (16/653)	3.8% (12/320)	-1.30% [-3.70%, 1.10%]
Cardiac Death or MI	2.9% (19/657)	3.8% (12/320)	-0.86% [-3.30%, 1.59%]	3.4% (22/653)	4.7% (15/320)	-1.32% [-4.02%, 1.38%]
Stent Thrombosis – Protocol defined	0.6% (4/654)	0.0% (0/319)	0.61% [Assump. not met]	0.8% (5/647)	0.6% (2/317)	0.14% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]	0.3% (2/667)	0.0% (0/330)	0.30% [Assump. not met]
Late (> 30 days)	0.2% (1/653)	0.0% (0/319)	0.15% [Assump. not met]	0.3% (2/646)	0.6% (2/317)	-0.32% [Assump. not met]

## Notes:

- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
  - 9 month and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively.
  - 9 months analysis results include 9 month events identified at the 1 year follow-up.
  - Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.
- <sup>1</sup>Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.  
<sup>2</sup>TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.  
<sup>3</sup>MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

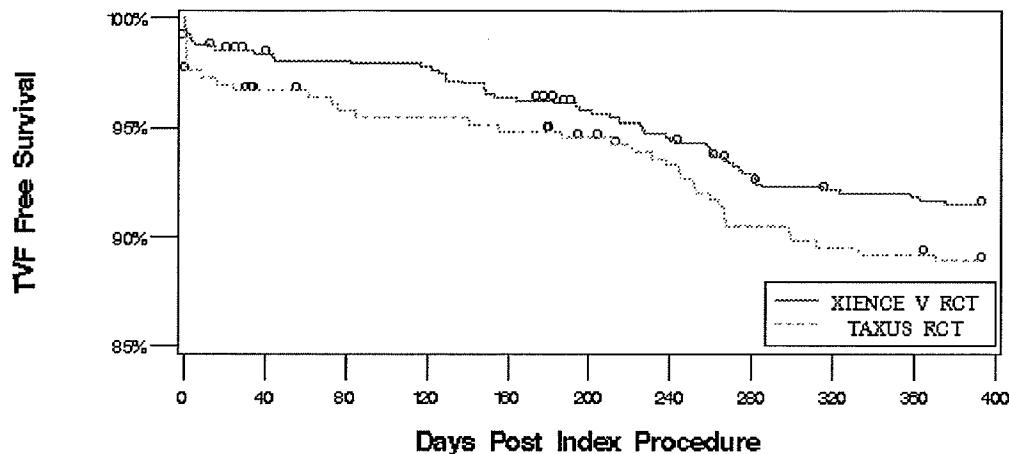
**Table 9.1.1-3: SPIRIT III 8 Month Angiographic and IVUS Results**

	XIENCE V (N=376) (M <sub>ANGIO</sub> =427) (M <sub>IVUS</sub> =181)	TAXUS (N=188) (M <sub>ANGIO</sub> =220) (M <sub>IVUS</sub> =93)	Difference [95% CI] <sup>1</sup>
<b>ANGIOGRAPHIC RESULTS</b>			
In-Stent MLD			
Post-Procedure	2.71 ± 0.43 (425)	2.74 ± 0.40 (220)	-0.03 [-0.10, 0.04]
8 Months	2.56 ± 0.53 (343)	2.45 ± 0.65 (158)	0.11 [-0.01, 0.23]
In-Segment MLD			
Post-Procedure	2.35 ± 0.44 (426)	2.36 ± 0.45 (220)	-0.01 [-0.08, 0.06]
8 Months	2.22 ± 0.53 (344)	2.12 ± 0.60 (158)	0.10 [-0.01, 0.21]
In-Stent %DS			
Post-Procedure	0.32 ± 8.86 (424)	-0.78 ± 10.65 (220)	1.10 [-0.55, 2.74]
8 Months	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-Segment %DS			
Post-Procedure	13.89 ± 8.04 (425)	13.92 ± 7.20 (220)	-0.03 [-1.26, 1.19]
8 Months	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
Late Loss			
In-Stent	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
In-Segment	0.14 ± 0.39 (343)	0.26 ± 0.46 (158)	-0.13 [-0.21, -0.04]
Binary Restenosis			
In-Stent	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-Segment	4.7% (16/344)	8.9% (14/158)	-4.21% [-9.17%, 0.75%]
<b>IVUS RESULTS</b>			
Neointimal Volume (mm <sup>3</sup> )	10.13 ± 11.46 (101)	20.87 ± 13.51 (41)	-10.74 [-20.92, -0.56]
% Volume Obstruction	6.91 ± 6.35 (98)	11.21 ± 9.86 (39)	-4.30 [-7.72, -0.88]
Incomplete Apposition			
Post Procedure	34.4% (31/90)	25.6% (11/43)	8.86% [-7.46%, 25.19%]
8 month	25.6% (23/90)	16.3% (7/43)	9.28% [-4.97%, 23.52%]
Persistent	24.4% (22/90)	14.0% (6/43)	10.49% [-3.15%, 24.13%]
Late Acquired	1.1% (1/90)	2.3% (1/43)	-1.21% [Assump. not met]

**Notes:**

- N is the total number of subjects; M<sub>ANGIO</sub> is the total number of lesions in the protocol required angiographic cohort and M<sub>IVUS</sub> is the total number of lesions in the protocol required IVUS cohort.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- 8 month time frame includes follow-up window (240 + 28 days).
- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

<sup>1</sup> Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

**Figure 9.1.1-1: SPIRIT III: Survival Free of Target Vessel Failure through 1 Year**

TVF	Event Free	Event Rate	P-value
XIENCE V	91.5%	8.5%	0.18
TAXUS	88.9%	11.1%	

**Note:**

- Time Frame includes follow-up window (365 + 28 days)

'P-value based on log rank and not adjusted for multiple comparisons

**Table 9.1.1-4: SPIRIT III RCT ARC defined Definite+Probable Stent Thrombosis Through 1 Year**

	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI] <sup>1</sup>
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	1.1% (7/648)	0.6% (2/317)	0.45% [Assump. not met]
Acute (< 1 day)	0.1% (1/669)	0.0% (0/330)	0.15% [Assump. not met]
Subacute (1 – 30 days)	0.4% (3/667)	0.0% (0/330)	0.45% [Assump. not met]
Late (> 30 days)	0.5% (3/647)	0.6% (2/317)	-0.17% [Assump. not met]

**Notes:**

- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.

- Time Frame includes follow-up window (365 + 28 days)

- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

<sup>1</sup> Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

### 9.1.2 SPIRIT III US 4.0 mm Arm

**Primary Objective:** The objective of the SPIRIT III 4.0 mm arm was to demonstrate the non-inferiority in in-segment late loss at 240 days compared to the TAXUS arm of the SPIRIT III RCT.

**Design:** The SPIRIT III 4.0 mm study was a prospective, single-arm, multi-center clinical trial in the United States evaluating the 4.0 mm diameter XIENCE V stent. Sixty-nine (69) subjects were enrolled in the SPIRIT III 4.0 mm study arm.

All subjects had clinical follow-up at 30, 180, 240, and 270 days, and annually from 1 to 5 years. In addition, all subjects had angiographic follow-up at 240 days. IVUS was performed for subjects who received a bailout stent at baseline and 240 days.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

**Demographics:** The mean age in the SPIRIT III 4.0 arm was 61.9 years with 72.5% (50/69) male, 21.7% (15/69) had prior cardiac interventions, and 30.4% (21/69) had a history of diabetes.

**Results:** The results are presented in Table 9.1.2-1 (Primary endpoints), Table 9.1.2-2 (Clinical Results), Table 9.1.2-3 (Angiographic Results), and Table 9.1.2-4 (ARC-Defined Stent Thrombosis). These analyses were performed on the intent to treat population.

The primary endpoint of in-segment late loss at 240 days was met with measurements of  $0.17 \pm 0.38$  mm (49) for the XIENCE V 4.0 mm arm and  $0.28 \pm 0.48$  mm (134) for the TAXUS arm from the SPIRIT III RCT ( $p < 0.0001$  for non-inferiority).

**Table 9.1.2-1: SPIRIT III 4.0 mm Primary Endpoints Results**

Measurements	XIENCE V (M=69)	TAXUS (M=188)	Difference [95% CI]	Non-Inferiority P-Value
8 Month Late Loss, In-segment (mm)	$0.17 \pm 0.38$ (49)	$0.28 \pm 0.48$ (134)	-0.11 [-0.24, 0.03] <sup>1</sup>	<0.0001 <sup>2</sup>

Notes:

- M is the total number of analysis lesions.
- One subject in SPIRIT III TAXUS arm did not provide written informed consent and was inadvertently randomized into the study. Data from this subject is excluded from all data analyses.
- Time Frame includes follow-up window (240 + 28 days)

<sup>1</sup>By normal approximation.

<sup>2</sup>One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195 mm, to be compared at a 0.038 significance level.

**Table 9.1.2-2: SPIRIT III 4.0 mm Clinical Results**

	OUTCOMES AT 9 MONTHS XIENCE V (N=69)	OUTCOMES AT 1 YEAR (latest available follow-up) XIENCE V (N=69)
<b>COMPOSITE EFFICACY &amp; SAFETY</b>		
TVF <sup>1</sup>	5.9% (4/68)	5.9% (4/68)
MACE <sup>2</sup>	5.9% (4/68)	5.9% (4/68)
<b>EFFICACY</b>		
Ischemia-Driven TLR	1.5% (1/68)	1.5% (1/68)
TLR, CABG	0.0% (0/68)	0.0% (0/68)
TLR, PCI	1.5% (1/68)	1.5% (1/68)
Ischemia-Driven non-TLR TVR	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, CABG	0.0% (0/68)	0.0% (0/68)
non-TLR TVR, PCI	0.0% (0/68)	0.0% (0/68)
<b>SAFETY</b>		
All Death	1.5% (1/68)	1.5% (1/68)
Cardiac Death	1.5% (1/68)	1.5% (1/68)
Non-Cardiac Death	0.0% (0/68)	0.0% (0/68)
MI	4.4% (3/68)	4.4% (3/68)
QMI	0.0% (0/68)	0.0% (0/68)
NQMI	4.4% (3/68)	4.4% (3/68)
Cardiac Death or MI	5.9% (4/68)	5.9% (4/68)
Stent Thrombosis – Protocol defined	1.5% (1/67)	1.5% (1/67)
Acute (< 1 day)	1.4% (1/69)	1.4% (1/69)
Subacute (1 – 30 days)	0.0% (0/69)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)	0.0% (0/67)

**Notes:**

<sup>1</sup> 9 months and 1 year time frames include follow-up window (270 +14 days and 365 + 28 days) respectively. 9 month analysis includes 9 month events identified at the 1 year follow-up.

<sup>1</sup> TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.

<sup>2</sup> MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

**Table 9.1.2-3: SPIRIT III 4.0 mm 8 Month Angiographic Results**

	XIENCE V (N=69) (M=69)
ANGIOGRAPHIC RESULTS	
In-Stent MLD	
Post-Procedure	3.46 ± 0.38 (69)
8 Months	3.36 ± 0.46 (49)
In-Segment MLD	
Post-Procedure	3.07 ± 0.43 (69)
8 Months	2.91 ± 0.51 (49)
In-Stent %DS	
Post-Procedure	2.12 ± 10.27 (69)
8 Months	4.78 ± 13.20 (49)
In-Segment %DS	
Post-Procedure	13.42 ± 8.08 (69)
8 Months	17.92 ± 10.83 (49)
Late Loss	
In-Stent	0.12 ± 0.34 (49)
In-Segment	0.17 ± 0.38 (49)
Binary Restenosis	
In-Stent	0.0% (0/49)
In-Segment	2.0% (1/49)

**Notes:**

- N is the total number of subjects; M is the total number of lesions at baseline.
- 8 month time frame includes follow-up window (240 + 28 days).

**Table 9.1.2-4: SPIRIT III 4.0 mm ARC defined Definite+Probable Stent Thrombosis Through 1 Year**

	XIENCE V (N=69)
ARC Definite+Probable Stent Thrombosis (0 days – 1 year)	0.0% (0/67)
Acute (< 1 day)	0.0% (0/69)
Subacute (1 – 30 days)	0.0% (0/69)
Late (> 30 days)	0.0% (0/67)

**Notes:**

- Time Frame includes follow-up window (365 + 28 days)

## 9.2 SPIRIT II Supportive Clinical Trial

**Primary Objective:** The objective of the SPIRIT II clinical study was to demonstrate the non-inferiority in in-stent late loss at 180 days of the XIENCE V stent to the TAXUS stent in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel. The SPIRIT II clinical study arm allowed the treatment of *de novo* lesions  $\leq 28$  mm in length in coronary arteries with a reference vessel diameter (RVD)  $\geq 2.5$  mm to  $\leq 4.25$  mm. If non-inferiority of in-stent late loss was demonstrated, it was pre-specified that testing for superiority could be conducted. SPIRIT II was performed outside of the U.S.

**Design:** The SPIRIT II clinical study was a prospective, active-control, 3:1 (XIENCE V:TAXUS) randomized, single-blind, multi-center non-inferiority evaluation of the XIENCE V stent compared to the TAXUS stent in the treatment of up to two de novo lesions  $\leq$  28 mm in length in native coronary arteries with RVD  $\geq$  2.5 mm to  $\leq$  4.25 mm. Given the available XIENCE V stent lengths of 8, 18 and 28 mm for this trial, in the XIENCE V arm, treatment of a target lesion  $>$  22 mm and  $\leq$  28 mm in length was accomplished by planned overlap of either two 18 mm stents or a 28 mm and an 8 mm stent. In the TAXUS arm, overlap was only permitted for bailout or to ensure adequate lesion coverage.

Three hundred (300) subjects were enrolled in the study at 28 international sites in Europe, India and New Zealand.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiographic follow-up at 180 days with planned additional angiographic and IVUS follow-up at 2 years in a pre-specified subgroup of 152 consecutively enrolled subjects at selected sites.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 6 months and aspirin daily to be taken throughout the length of the trial (5 years).

A subgroup of 39 subjects were enrolled in a pharmacokinetic (PK) substudy. Venous blood was drawn at regular intervals for PK analysis of total blood everolimus level at 7 pre-determined sites.

**Demographics:** The mean age was 62.0 years for the XIENCE V arm and 61.9 years for the TAXUS arm. The XIENCE V had 70.9% (158/223) males and the TAXUS arm had 79.2% (61/77) males. The XIENCE V arm had 23.3% (52/223) of subjects with prior cardiac interventions and the TAXUS arm had 22.1% (17/77). The XIENCE V arm had 22.9% (51/223) of subjects with a history of diabetes and the TAXUS arm had 23.7% (18/76). The XIENCE V had 16.6% (37/223) of subjects with a lesion treated in two vessels and TAXUS had 18.2% (14/77). The XIENCE V arm had 10.8% (24/223) of subjects with planned stent overlap. The XIENCE V arm had 18.4% (40/217) of subjects with a history of an MI within two months while the TAXUS arm had 7.8% (6/77) ( $p=0.0284$ ). The remaining subject baseline clinical features were well-matched between the XIENCE V arm and the TAXUS arm.

**Results:** The results are presented in Table 9.2-1 (Primary endpoint), Table 9.2-2 (Clinical Results), Table 9.2-3 (Angiographic and IVUS Results), and Table 9.2-4 (ARC-Defined Stent Thrombosis). These analyses were based on the intent to treat population.

The primary endpoint of in-stent late loss at 180 days was met with measurements of  $0.11 \pm 0.27$  mm (201) for the XIENCE V arm and  $0.36 \pm 0.39$  mm (73) for the TAXUS arm ( $p < 0.0001$  for non-inferiority). In a prespecified analysis, the XIENCE V stent was shown to be superior to the TAXUS stent with respect to in-stent late loss at 180 days ( $p < 0.0001$ ).

**Table 9.2-1: SPIRIT II Primary Endpoint Result**

<b>Measurements</b>	<b>XIENCE V (N=223) (M=201)</b>	<b>TAXUS (N=77) (M=73)</b>	<b>Difference [95% CI]</b>	<b>Non-Inferiority P-Value</b>	<b>Superiority P-Value</b>
<b>180 Day Late Loss, In-stent (mm)</b>	<b>0.11 ± 0.27 (201)</b>	<b>0.36 ± 0.39 (73)</b>	<b>-0.24 [-0.34, -0.15]<sup>1</sup></b>	<b>&lt;0.0001<sup>2</sup></b>	<b>&lt;0.0001<sup>3</sup></b>

**Notes:**

– N is the number of subjects and M is the total number of analysis lesions.

<sup>1</sup> By normal approximation.

<sup>2</sup> One-sided p-value by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.16 mm, to be compared at a 0.0448 significance level.

<sup>3</sup> P-value from two-sided t-test.

**Table 9.2-2: SPIRIT II Clinical Results**

	OUTCOMES AT 6 MONTHS			OUTCOMES AT 2 YEARS (latest available follow-up)		
	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI] <sup>1</sup>	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI] <sup>1</sup>
<b>COMPOSITE EFFICACY &amp; SAFETY</b>						
TVF <sup>2</sup>	3.6% (8/222)	6.5% (5/77)	-2.89% [-8.92%, 3.14%]	10.0% (21/211)	12.3% (9/73)	-2.38% [-10.93%, 6.18%]
MACE <sup>3</sup>	2.7% (6/222)	6.5% (5/77)	-3.79% [-9.69%, 2.11%]	6.6% (14/211)	11.0% (8/73)	-4.32% [-12.24%, 3.59%]
<b>EFFICACY</b>						
Ischemia-Driven TLR	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
TLR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
TLR, PCI	1.8% (4/222)	3.9% (3/77)	-2.09% [Assump. not fulfilled]	3.8% (8/211)	6.8% (5/73)	-3.06% [-9.40%, 3.28%]
Ischemia-Driven non-TLR TVR	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.8% (8/211)	4.1% (3/73)	-0.32% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.5% (1/211)	0.0% (0/73)	0.47% [Assump. not met]
non-TLR TVR, PCI	0.9% (2/222)	1.3% (1/77)	-0.40% [Assump. not fulfilled]	3.3% (7/211)	4.1% (3/73)	-0.79% [Assump. not met]
<b>SAFETY</b>						
All Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.7% (8/218)	6.5% (5/77)	-2.82% [-8.87%, 3.22]
Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	0.5% (1/218)	1.3% (1/77)	-0.84% [Assump. not met]
Non-Cardiac Death	0.0% (0/222)	1.3% (1/77)	-1.30% [Assump. not fulfilled]	3.2% (7/218)	5.2% (4/77)	-1.98% [Assump. not met]
MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
QMI	0.0% (0/222)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/211)	0.0% (0/73)	0.00% [Assump. not met]
NQMI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	2.8% (6/211)	5.5% (4/73)	-2.64% [Assump. not met]
Cardiac Death or MI	0.9% (2/222)	3.9% (3/77)	-3.00% [Assump. not fulfilled]	3.3% (7/211)	5.5% (4/73)	-2.16% [Assump. not met]
Stent Thrombosis – Protocol defined	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]
Acute (< 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not fulfilled]	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Late (> 30 days)	0.5% (1/222)	1.3% (1/77)	-0.85% [Assump. not fulfilled]	1.9% (4/211)	1.4% (1/73)	0.53% [Assump. not met]

## Notes:

– 6 months and 2 year time frames include follow-up window (180 +14 days and 730 + 28 days).

– Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

<sup>1</sup> Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.<sup>2</sup> TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.<sup>3</sup> MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

**Table 9.2-3: SPIRIT II 180-Day Angiographic and IVUS Results**

	XIENCE V (N=223) (M=260)	TAXUS (N=77) (M=91)	Difference [95% CI] <sup>1</sup>
<b>ANGIOGRAPHIC RESULTS</b>			
In-Stent MLD			
Post-Procedure	2.49 ± 0.40 (260)	2.62 ± 0.45 (91)	-0.13 [-0.24, -0.03]
6 Months	2.38 ± 0.50 (237)	2.27 ± 0.54 (86)	0.10 [-0.03, 0.23]
In-Segment MLD			
Post-Procedure	2.15 ± 0.44 (260)	2.22 ± 0.53 (91)	-0.07 [-0.19, 0.05]
6 Months	2.10 ± 0.51 (237)	2.08 ± 0.54 (86)	0.02 [-0.11, 0.15]
In-Stent %DS			
Post-Procedure	13.01 ± 6.02 (260)	12.66 ± 5.53 (91)	0.35 [-1.01, 1.71]
6 Months	15.70 ± 9.88 (237)	20.89 ± 11.59 (86)	-5.18 [-7.96, -2.41]
In-Segment %DS			
Post-Procedure	22.51 ± 8.98 (260)	23.36 ± 11.20 (91)	-0.86 [-3.43, 1.72]
6 Months	23.61 ± 11.65 (237)	27.05 ± 12.68 (86)	-3.44 [-6.53, -0.35]
Late Loss			
In-Stent	0.12 ± 0.29 (237)	0.37 ± 0.38 (86)	-0.25 [-0.34, -0.16]
In-Segment	0.07 ± 0.33 (237)	0.15 ± 0.38 (86)	-0.08 [-0.17, 0.01]
Binary Restenosis			
In-Stent	1.3% (3/237)	3.5% (3/86)	-2.22% [Assump. not met]
In-Segment	3.4% (8/237)	5.8% (5/86)	-2.44% [-7.89%, 3.02%]
<b>IVUS RESULTS</b>			
Neointimal Volume (mm <sup>3</sup> )	3.83 ± 6.55 (99)	14.42 ± 16.03 (40)	-10.60 [-15.87, -5.32]
% Volume Obstruction	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	-4.85 [-7.27, -2.42]
Incomplete Apposition			
Post Procedure	6.5% (7/108)	5.6% (2/36)	0.93% [Assump. not met]
6 month	2.9% (3/103)	0.0% (0/39)	2.91% [Assump. not met]
Persistent	2.5% (3/120)	0.0% (0/42)	2.50% [Assump. not met]
Late Acquired	0.0% (0/104)	0.0% (0/39)	0.00% [Assump. not met]

## Notes:

- N is the total number of subjects; M is the total number of lesions.
  - Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.
- <sup>1</sup> Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

**Table 9.2-4: SPIRIT II ARC defined Definite+Probable Stent Thrombosis Through 2 Years**

	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI]
ARC Definite+Probable Stent Thrombosis (0 days – 2 years)	0.9% (2/211)	1.4% (1/73)	-0.42% [Assump. not met]
Acute ( < 1 day)	0.0% (0/223)	0.0% (0/77)	0.00% [Assump. not met]
Subacute ( 1 – 30 days)	0.0% (0/223)	1.3% (1/77)	-1.30% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/220)	1.3% (1/77)	-1.30% [Assump. not met]
Very Late (1 – 2 years)	0.9% (2/211)	0.0% (0/72)	0.95% [Assump. not met]

Note:

– Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

<sup>1</sup> Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

### 9.3 SPIRIT FIRST Randomized Clinical Trial

**Objective:** The objective of the SPIRIT FIRST randomized clinical trial was to assess the feasibility and performance of the XIENCE V stent (called VISION-E within the SPIRIT FIRST study) in the treatment of subjects with a single *de novo* native coronary artery lesion with reference vessel diameter (RVD) of 3.0 mm and lesion length ≤ 12 mm. This study compared the XIENCE V stent to a matched uncoated metallic stent control (MULTI-LINK VISION).

**Design:** SPIRIT FIRST was a single-blind multi-center randomized controlled trial to assess the safety and performance of everolimus eluting from a durable polymer on a cobalt chromium stent (XIENCE V stent). Sixty (60) subjects were enrolled in the study.

All subjects had clinical follow-up at 30, 180, and 270 days, and annually from 1 to 5 years. All subjects had angiography and IVUS at baseline and at 180 days and 1 year follow-up.

Following the index procedure, all subjects were to be maintained on clopidogrel bisulfate daily for a minimum of 3 months and aspirin daily to be taken throughout the length of the trial (1 year).

**Demographics:** The mean age was 64.2 years for the XIENCE V arm and 61.4 years for the VISION arm. The XIENCE V had 70.4% (19/27) males and the VISION arm had 75.9% (22/29) males. The XIENCE V arm had 18.5% (5/27) subjects with prior cardiac interventions and the VISION arm had 6.9% (2/29). The XIENCE V arm had 11.1% (3/27) subjects with a history of diabetes and the VISION arm had 10.3% (3/29). XIENCE V arm had 70.4% (19/27) of subjects with hypertension requiring medication while the VISION arm had 41.4% (12/29) ( $p=0.035$ ). The remaining subject baseline clinical features were also well-matched between the XIENCE V arm and the VISION arm.

**Results:** The results are presented in Table 9.3-1 (Primary endpoint), Table 9.3-2 (Clinical Results), Table 9.3-3 (Angiographic and IVUS Results), and Table 9.3-4 (ARC-Defined Stent Thrombosis). These analyses were based on the per protocol evaluable population.

The primary superiority endpoint of in-stent late loss at 180 days was met with measurements of  $0.10 \pm 0.23$  mm (23) for the XIENCE V arm and  $0.85 \pm 0.36$  mm (27) for the MULTI-LINK VISION arm ( $p < 0.0001$ ).

Table 9.3-1: SPIRIT FIRST Primary Endpoint Result

Measurements	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI] <sup>1</sup>	Superiority P-value <sup>2</sup>
180 Days Late Loss, In-stent (mm)	$0.10 \pm 0.23$ (23)	$0.85 \pm 0.36$ (27)	-0.76 [-0.93, -0.59] <sup>1</sup>	< 0.0001

Note: N is the number of subjects.

<sup>1</sup> By normal approximation

<sup>2</sup> One-tailed p-value by t-test, to be compared to a 5% significance level

Table 9.3-2: SPIRIT FIRST Clinical Results

	OUTCOMES AT 6 MONTHS <sup>1</sup>			OUTCOMES AT 3 YEARS <sup>1</sup> (latest available follow-up)		
	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI] <sup>2</sup>	XIENCE V (N = 27)	VISION (N = 29)	Difference [98% CI] <sup>3</sup>
<b>COMPOSITE EFFICACY &amp; SAFETY</b>						
TVF <sup>3</sup>	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]	15.4% (4/26)	32.1% (9/28)	-16.76% [Assump. not met]
MACE <sup>4</sup>	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]	15.4% (4/26)	25.0% (7/28)	-9.62% [Assump. not met]
<b>EFFICACY</b>						
Ischemia-Driven TLR	3.8% (1/26)	21.4% (6/28)	-17.58% [Assump. not met]	7.7% (2/26)	25.0% (7/28)	-17.31% [Assump. not met]
TLR, CABG	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
TLR, PCI	3.8% (1/26)	17.9% (5/28)	-14.01% [Assump. not met]	7.7% (2/26)	21.4% (6/28)	-13.74% [Assump. not met]
Ischemia-Driven non-TLR TVR	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	10.7% (3/28)	-10.71% [Assump. not met]
non-TLR TVR, CABG	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	3.6% (1/28)	-3.57% [Assump. not met]
non-TLR TVR, PCI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	7.1% (2/28)	-7.14% [Assump. not met]
<b>SAFETY</b>						
All Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Non-Cardiac Death	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
QMI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
NQMI	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]
Cardiac Death or MI	3.8% (1/26)	0.0% (0/28)	3.85% [Assump. not met]	7.7% (2/26)	0.0% (0/28)	7.69% [Assump. not met]
Stent Thrombosis – Protocol defined	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]	0.0% (0/27)	0.0% (0/29)	0.00% [Assump. not met]
Late (> 30 days)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

**Note:**<sup>1</sup> Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.<sup>1</sup> 6 month and 3 year time frames include follow-up window (180 +14 days and 1095 + 28 days) respectively.<sup>2</sup> Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.<sup>3</sup> TVF is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR and ischemic-driven non-TLR TVR.<sup>4</sup> MACE is defined as a hierarchical composite of cardiac death, MI, ischemic-driven TLR.

**Table 9.3-3: SPIRIT FIRST 180-Day Angiographic and IVUS Results**

	XIENCE V (N = 27)	VISION (N = 29)	Difference [95% CI] <sup>1</sup>
<b>ANGIOGRAPHIC RESULTS</b>			
In-Stent MLD			
Post-Procedure	2.34± 0.26 (27)	2.43± 0.30 (29)	-0.09 [-0.24, 0.06]
6 Months	2.28± 0.33 (23)	1.58± 0.41 ( 27)	0.70 [0.49,0.91]
In-Segment MLD			
Post-Procedure	2.07± 0.37 ( 27)	2.15± 0.37 ( 29)	-0.08 [-0.28, 0.12.]
6 Months	2.04 ± 0.40 ( 23)	1.54± 0.41 ( 27)	0.50 [0.27, 0.73]
In-Stent %DS			
Post-Procedure	12.34 ± 4.02 ( 27)	14.85 ± 4.76 ( 29)	-2.51 [-4.87, -0.16]
6 Months	15.57 ± 7.64 ( 23)	38.61 ± 14.25 ( 27)	-23.05 [-29.45, -16.64]
In-Segment %DS			
Post-Procedure	20.82 ± 7.65 (27)	23.14 ± 8.03% (29)	-2.32 [-6.52, 1.88]
6 Months	21.89 ± 11.15 (23)	40.78 ± 13.67 (27)	-18.89 [-25.95,-11.83]
Late Loss			
In-Stent	0.10 ± 0.23 (23)	0.85 ± 0.36 (27)	-0.76 [-0.93, -0.59]
In-Segment	0.09 ± 0.20 (23)	0.61 ± 0.37 (27)	-0.53 [-0.69, -0.36]
Binary Restenosis			
In-Stent	0.0% (0/23)	25.9% (7/27)	-25.93% [Assump. not met]
In-Segment	4.3% (1/23)	33.3% (9/27)	-28.99% [Assump. not met]
<b>IVUS RESULTS</b>			
Neointimal Volume (mm <sup>3</sup> )	10.29± 13.32 ( 21)	38.29± 19.08 ( 24)	-28.00 [-37.82, -18.19]
% Volume Obstruction	7.95± 10.44 ( 21)	28.11± 13.98 ( 24)	-20.16 [-27.53, -12.79]
Incomplete Apposition			
Post Procedure	0.0% ( 0/ 27)	10.7% ( 3/ 28)	-10.71% [Assump. not met]
6 month	0.0% ( 0/ 21)	0.0% ( 0/ 22)	0.00% [Assump. not met]
Persistent	0.0% ( 0/ 27)	0.0% ( 0/ 28)	0.00% [Assump. not met]
Late Acquired	0.0% ( 0/ 21)	0.0% ( 0/ 22)	0.00% [Assump. not met]

**Note:**

<sup>1</sup> Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

<sup>1</sup> Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

**Table 9.3-4: SPIRIT FIRST ARC defined Definite+Probable Stent Thrombosis Through 3 Years**

	XIENCE V (N=27)	VISION (N=29)	Difference [95% CI] <sup>1</sup>
ARC Definite+Probable Stent Thrombosis (0 days – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Acute (< 1 day)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Subacute (1 – 30 days)	0.0% (0/27)	0.0% (0/28)	0.00% [Assump. not met]
Late (31 days – 1 year)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]
Very Late (1 – 3 years)	0.0% (0/26)	0.0% (0/28)	0.00% [Assump. not met]

Note:

- Assump. not met means that assumption of normal approximation not met due to small sample size or frequency of events.

<sup>1</sup> Confidence Interval was calculated using the normal approximation, not adjusted for multiplicity and is meant for descriptive purposes only.

#### 9.4 SPIRIT II and SPIRIT III Pooled Analysis

In order to better estimate the incidence of low frequency events or outcomes in various specific subject subgroups, a subject-level pooled analysis was conducted of both randomized trials comparing the XIENCE V stent versus the TAXUS stent. Data from the SPIRIT II and SPIRIT III clinical trials were pooled to compare the XIENCE V stent to the TAXUS control stent in 1302 subjects out to 1 year (393 days) of follow-up. These two studies have subjects with similar baseline and angiographic characteristics and the key elements of study design including inclusion and exclusion criteria and endpoint definitions are comparable. The subject level data were included until the latest available time point of 1 year for each trial. Table 9.4-1 shows the subject disposition over time for the SPIRIT II and III RCT. The percentage of the total number of subjects that were enrolled in the studies and completed their 1 year follow-up was 96.5%.

**Table 9.4-1: Subject Disposition Table (N=1302; SPIRIT II and SPIRIT III RCT)**

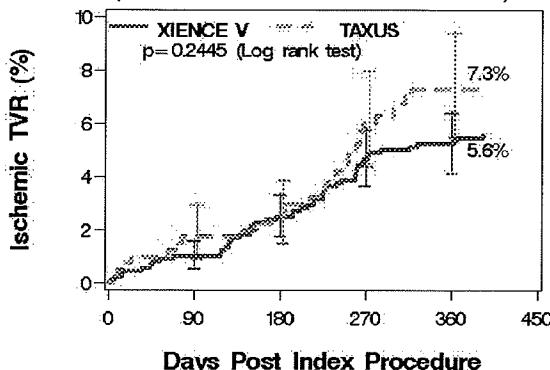
Subjects	30-Day Follow-up		9-Month Follow-up		1-Year Follow-up	
	XIENCE V (890)		XIENCE V (873)		XIENCE V (866)	
	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
Subjects	223	667	220	653	220	646
	TAXUS (407)		TAXUS (395)		TAXUS (392)	
Subjects	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III	SPIRIT II	SPIRIT III
	77	330	76	319	76	316

It is acknowledged that these retrospective pooled analyses are exploratory and hypothesis-generating. Definitive proof of the presence or absence of any differences between such sub-groups requires prospectively powered assessment in dedicated clinical trials. The pooled analysis from SPIRIT II and SPIRIT III trials includes subjects from single-blind trials with similar inclusion and exclusion criteria in 1,302 subjects with 1,506 lesions.

As shown in Figure 9.4-1, at one year, the analyses of pooled trials suggest a reduction in the rates of TVR and TLR for the XIENCE V stent compared to the TAXUS stent through one year. All CI bars represent a 1.5 standard error.

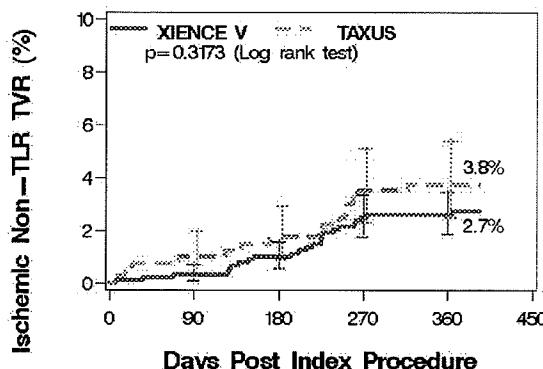
**Figure 9.4-1: Kaplan Meier Hazard Curves for Time to First TVR or TLR Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)**

**TVR (Includes TLR and Non-TLR TVR)**



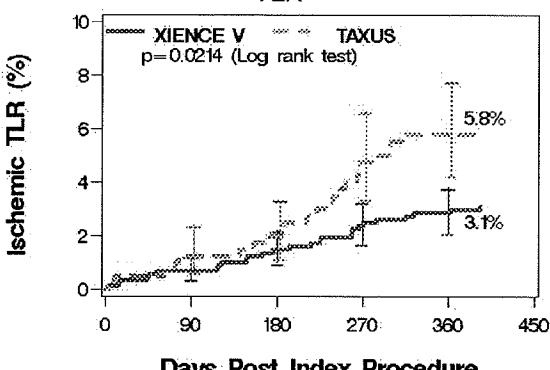
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

**Non-TLR TVR**



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

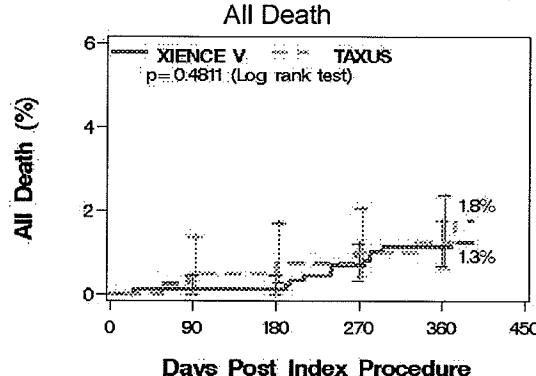
**TLR**



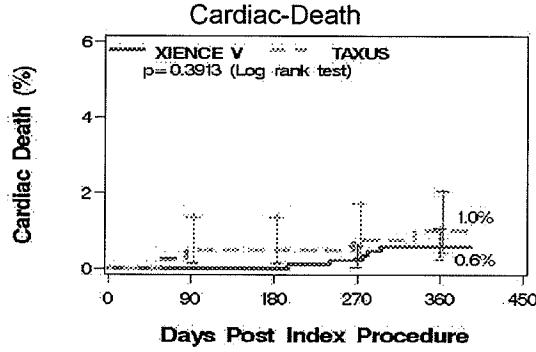
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of all death, cardiac death, and non-cardiac death through 1 year are shown in Figure 9.4-2.

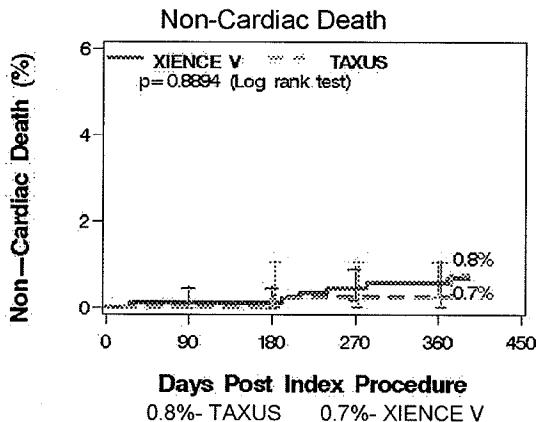
**Figure 9.4-2: Kaplan Meier Hazard Curves for Time to Death through 393 Days  
(Pooled SPIRIT II and SPIRIT III RCTs)**



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

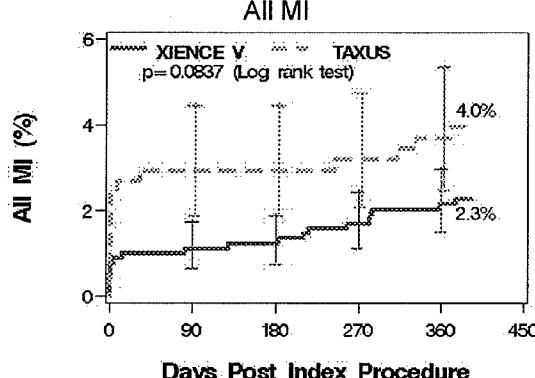


0.8%- TAXUS 0.7%- XIENCE V

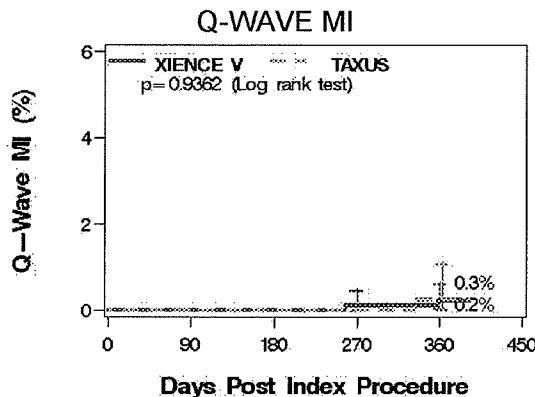
Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

Pooled analyses of the rates of MIs through 1 year are shown in Figure 9.4-3.

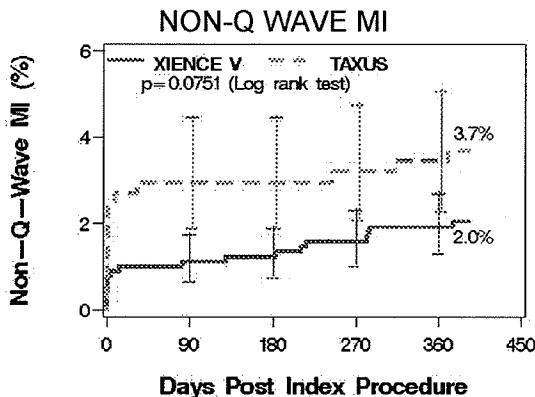
**Figure 9.4-3: Kaplan Meier Hazard Curves for Time to First MI Event through 393 Days  
(Pooled SPIRIT II and SPIRIT III RCTs)**



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.



Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

#### 9.4.1 Stent Thrombosis in SPIRIT II and SPIRIT III Pooled Analysis

The results for the pooled analysis rates of stent thrombosis at one year are shown below in Figure 9.4.1-1. Rates were low for both treatments in this pooled analysis and consistent with the published literature<sup>10</sup>. The rates of stent thrombosis were evaluated based on the SPIRIT II and III protocol defined definition and the ARC definition for definite + probable thrombosis (see definitions above in Section 8.2). These data are presented in table 9.4.1-1.

**Table 9.4.1-1 Pooled Results for Stent Thrombosis through 1 year  
(SPIRIT II and SPIRIT III RCT)**

	XIENCE V (N=892)	95% CI <sup>1</sup>	TAXUS (N=410)	95% CI <sup>1</sup>
<b>0 - 30 days</b>				
Protocol	0.3% (3/890)	[0.07%, 0.98%]	0.0% (0/407)	[0.00%, 0.90%]
ARC (definite + probable)	0.4% (4/890)	[0.12%, 1.15%]	0.2% (1/407)	[0.01%, 1.36%]
<b>31 days – 1 year</b>				
Protocol	0.3% (3/866)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.3% (3/867)	[0.07%, 1.01%]	0.8% (3/394)	[0.16%, 2.21%]
<b>0 – 1 year</b>				
Protocol	0.7% (6/867)	[0.25%, 1.50%]	0.8% (3/394)	[0.16%, 2.21%]
ARC (definite + probable)	0.8% (7/868)	[0.32%, 1.65%]	0.8% (3/394)	[0.16%, 2.21%]

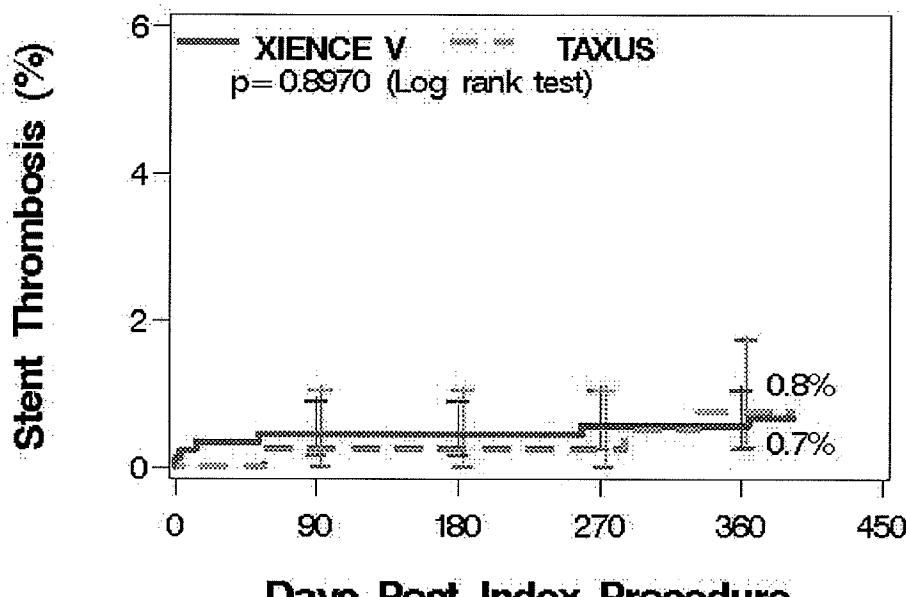
Note: timeframe for 1 year includes the follow-up window (365 + 28 days)

<sup>1</sup> By Clopper-Pearson Exact Confidence Interval

<sup>10</sup> Ellis SG CA, Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol.* 2007;49:1043-1051.

**Figure 9.4.1-1: Kaplan Meier Hazard Curves for Time to First Stent Thrombosis Event through 393 Days (Pooled SPIRIT II and SPIRIT III RCTs)**

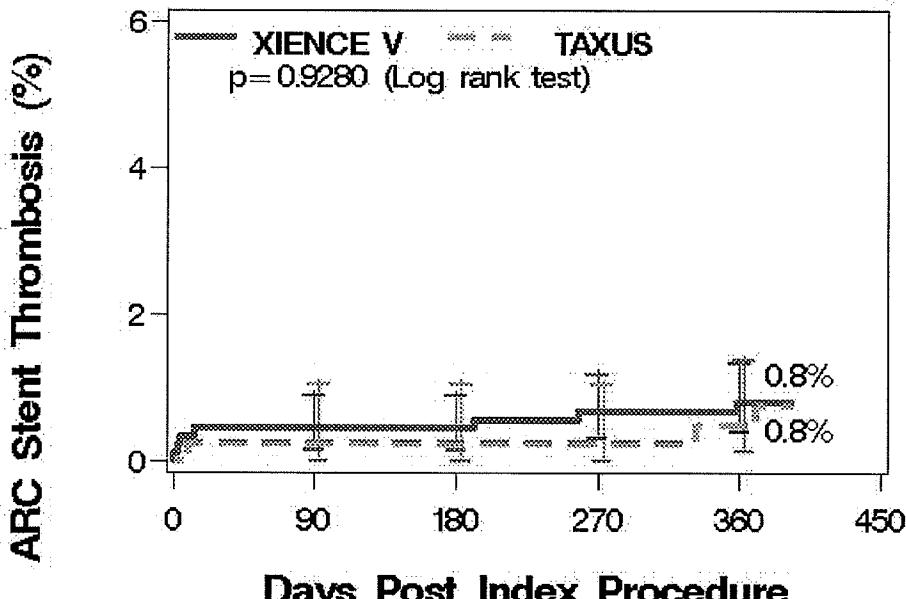
Protocol Defined Stent Thrombosis



### Days Post Index Procedure

Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

ARC DEFINED STENT THROMBOSIS (DEFINITE + PROBABLE)



### Days Post Index Procedure

Note: P-value is not adjusted for multiplicity and is meant for descriptive purposes only.

#### 9.4.2 Diabetics in SPIRIT II and SPIRIT III Pooled Analysis

Diabetic subjects comprise an important subject subgroup that is at increased risk for cardiovascular morbidity and mortality. Although diabetic subjects were included in the SPIRIT family of trials, there were no pre-specified hypotheses or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in diabetic individuals.

Table 9.4.2-1 shows the clinical outcomes through 1 year in subjects pooled from SPIRIT II and III. The randomization was stratified by history of diabetes to assure a balance between the XIENCE V and TAXUS treatment arms. In XIENCE V patients, there were numerically higher event rates in diabetics compared with non-diabetics. The event rates for TAXUS in diabetics were lower than the event rates for TAXUS non-diabetics. Given the relatively small sample size of the diabetic population and potential for confounding variables, no conclusions can be drawn from these post-hoc analyses.

**Table 9.4.2-1: Clinical Results in Diabetics and Non-Diabetics through 1 year  
(SPIRIT II and SPIRIT III RCT Pooled Population)**

	Non-Diabetics XIENCE V (N=643)	Non-Diabetics TAXUS (N=296)	All Diabetics XIENCE V (N=249)	All Diabetics TAXUS (N=110)
TLR	2.5% (16/629)	7.6% (22/290)	4.5% (11/244)	1.0% (1/104)
TVR(CABG/PCI), non TL	2.5% (16/629)	4.1% (12/290)	3.3% (8/244)	2.9% (3/104)
All Death	1.0% (6/631)	2.4% (7/291)	2.0% (5/246)	0.0% (0/104)
Cardiac Death	0.3% (2/631)	1.4% (4/291)	1.2% (3/246)	0.0% (0/104)
Non-Cardiac Death	0.6% (4/631)	1.0% (3/291)	0.8% (2/246)	0.0% (0/104)
MI	1.4% (9/629)	4.5% (13/290)	4.5% (11/244)	2.9% (3/104)
Cardiac Death or MI	1.7% (11/629)	5.2% (15/290)	5.3% (13/244)	2.9% (3/104)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.0% (3/287)	1.3% (3/240)	0.0% (0/104)
ARC definite + probable	0.3% (2/627)	0.7% (2/287)	2.1% (5/241)	1.0% (1/104)

**Table 9.4.2-2: Clinical Results in Diabetics through 1 year  
(SPIRIT II and SPIRIT III RCT Pooled Population – XIENCE V Subjects)**

	Non-Diabetics (N=643)	All Diabetics (N=249)	Insulin-Dependent Diabetics (N=63)	Non-Insulin-Dependent Diabetics (N=186)
TLR	2.5% (16/629)	4.5% (11/244)	6.5% (4/62)	3.8% (7/182)
TVR(CABG/PCI), non TL	2.5% (16/629)	3.3% (8/244)	1.6% (1/62)	3.8% (7/182)
All Death	1.0% (6/631)	2.0% (5/246)	3.2% (2/63)	1.6% (3/183)
Cardiac Death	0.3% (2/631)	1.2% (3/246)	1.6% (1/63)	1.1% (2/183)
Non-Cardiac Death	0.6% (4/631)	0.8% (2/246)	1.6% (1/63)	0.5% (1/183)
MI	1.4% (9/629)	4.5% (11/244)	9.7% (6/62)	2.7% (5/182)
Cardiac Death or MI	1.7% (11/629)	5.3% (13/244)	9.7% (6/62)	3.8% (7/182)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.3% (3/240)	1.6% (1/61)	1.1% (2/179)
ARC definite + probable	0.3% (2/627)	2.1% (5/241)	1.6% (1/61)	2.2% (4/180)

#### **9.4.3 Dual Vessel treatment in SPIRIT II and SPIRIT III Pooled Analysis**

Subjects requiring treatment in more than one vessel comprise a subgroup that is at increased risk for cardiovascular events compared with single vessel disease patients. Although subjects requiring both single and dual vessel treatment were included in the SPIRIT family of trials, there were no pre-specified hypothesis or trial features that warrant a specific labeled indication for the use of the XIENCE V stent in dual vessel individuals.

Table 9.4.3-1 shows the clinical outcomes through 1 year in subjects pooled from SPIRIT II and III. The randomization was stratified by the number of vessels treated to assure a balance between the XIENCE V and TAXUS treatment arms. Numerically lower event rates were observed for XIENCE V and TAXUS in single compared to dual vessel treatment. However, given the small sample size for dual vessel treatment, no conclusions can be drawn from this post-hoc analysis.

**Table 9.4.3-1: Clinical Results in Single and Dual Vessel Treatment through 1 year  
(SPIRIT II and SPIRIT III RCT Pooled Population)**

	Single Vessel XIENCE V (N=752)	Single Vessel TAXUS (N=344)	Dual Vessel XIENCE V (N=140)	Dual Vessel TAXUS (N=65)
TLR	2.9% (21/735)	4.5% (15/333)	4.3% (6/138)	12.5% (8/64)
TVR(CABG/PCI), non TLR	2.3% (17/735)	2.1% (7/333)	5.1% (7/138)	12.5% (8/64)
All Death	1.5% (11/739)	1.2% (4/333)	0.0% (0/138)	4.6% (3/65)
Cardiac Death	0.7% (5/739)	0.6% (2/333)	0.0% (0/138)	3.1% (2/65)
Non-Cardiac Death	0.8% (6/739)	0.6% (2/333)	0.0% (0/138)	1.5% (1/65)

	Single Vessel XIENCE V (N=752)	Single Vessel TAXUS (N=344)	Dual Vessel XIENCE V (N=140)	Dual Vessel TAXUS (N=66)
MI	1.9% (14/735)	3.0% (10/333)	4.3% (6/138)	9.4% (6/64)
Cardiac Death or MI	2.4% (18/735)	3.3% (11/333)	4.3% (6/138)	10.9% (7/64)
Stent Thrombosis				
Protocol defined	0.3% (2/729)	0.6% (2/332)	2.9% (4/138)	1.6% (1/62)
ARC definite + probable	0.5% (4/730)	0.6% (2/332)	2.2% (3/138)	1.6% (1/62)

## 10.0 INDIVIDUALIZATION OF TREATMENT

The risks and benefits should be considered for each patient before using the PROMUS stent. Patient selection factors to be assessed should include a judgment regarding risk of long-term antiplatelet therapy. Stenting is generally avoided in those patients at a heightened risk of bleeding (e.g., patients with recently active gastritis or peptic ulcer disease) in which anticoagulation therapy would be contraindicated.

Antiplatelet drugs should be used in combination with the PROMUS stent. Physicians should use information from the SPIRIT Clinical trials, coupled with current drug eluting stent (DES) literature and the specific needs of individual patients to determine the specific antiplatelet/anticoagulation regimen to be used for their patients in general practice. See also 5.2 – Precautions, Pre- and Post-Procedure Antiplatelet Regimen, Section 5.6 – Precautions, Use in Special Populations and Section 5.7 – Precautions, Lesion/Vessel Characteristics.

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

## 11.0 PATIENT COUNSELING AND PATIENT INFORMATION

Physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with stent placement.
- Discuss the risks associated with an everolimus-eluting stent.
- Discuss the risks of early discontinuation of the antiplatelet therapy.
- Discuss the risks of late stent thrombosis with DES use in higher risk patient subgroups.
- Discuss the risk/benefit issues for this particular patient.
- Discuss alteration to current life-style immediately following the procedure and over the long term.

The following patient materials are available for this product:

- A Patient Information Guide which includes information on coronary artery disease, the implant procedure and the PROMUS Everolimus-Eluting Coronary Stent System (provided to physician, on-line at [www.bostonscientific.com/promus](http://www.bostonscientific.com/promus), or by calling customer service 1-888-272-1001).
- A Stent Implant Card that includes both patient information and stent implant information (provided in package)

## 12.0 HOW SUPPLIED

**Sterile:** This device is sterilized with ethylene oxide gas, non-pyrogenic. It is intended for single use only. Do not resterilize. Do not use if the package is opened or damaged.

**Contents:** One (1) PROMUS Everolimus-Eluting Coronary Stent System, one (1) Flushing tool, (for the PROMUS EECSS Rapid Exchange (RX) Stent System), one (1) Stent Implant Card, one (1) Patient Information Guide.

**Storage:** Store in a dry, dark, cool place. Protect from light. Do not remove from carton until ready for use. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

## 13.0 OPERATOR'S INSTRUCTIONS

### 13.1 Inspection Prior to Use

- Carefully inspect the sterile package before opening and check for damage to the sterile barrier. Do not use if the integrity of the sterile package has been compromised.
- Do not use after the "Use By" date.
- Tear open the foil pouch and remove the inner pouch. **Note: the outside of the inner pouch is NOT sterile.** Open the inner pouch and pass or drop the product into the sterile field using an aseptic technique.
- Prior to using the PROMUS Everolimus-Eluting Coronary Stent System, carefully remove the system from the package and inspect for bends, kinks, and other damage. Verify that the stent does not extend beyond the radiopaque balloon markers. Do not use if any defects are noted. However, **do not manipulate, touch, or handle the stent** with your fingers, which may cause coating damage, contamination or stent dislodgement from the delivery balloon.

**Note:** At any time during use of the PROMUS Rapid Exchange (RX) EECSS, if the stainless steel proximal shaft has been bent or kinked, do not continue to use the catheter.

### 13.2 Materials Required

- Appropriate guiding catheter(s). See Table 1-1, PROMUS Stent System Product Description
- 2 – 3 syringes (10 – 20 ml)
- 1,000 u/500 ml Heparinized Normal Saline (HepNS)
- 0.014 inch (0.36 mm) x 175 cm (minimum length) guide wire
- Rotating hemostatic valve with appropriate minimum inner diameter [0.096 inch (2.44 mm)]
- 60% contrast diluted 1:1 with heparinized normal saline
- Inflation device

- Pre-deployment dilatation catheter
- Three-way stopcock
- Torque device
- Guide wire introducer
- Appropriate arterial sheath
- Appropriate anticoagulation and antiplatelet drugs

### 13.3 Preparation

#### 13.3.1 Packaging Removal

**Note:** The foil pouch is not a sterile barrier. The inner header bag (pouch) within the foil pouch is the sterile barrier. Only the contents of the inner pouch should be considered sterile. The outside surface of the inner pouch is NOT sterile.

1. Carefully remove the delivery system from its protective tubing for preparation of the delivery system. When using a Rapid Exchange (RX) system, do not bend or kink the hypotube during removal.
2. Remove the product mandrel and protective stent sheath by grasping the catheter just proximal to the stent (at the proximal balloon bond site), and with the other hand, grasp the stent protector and gently remove distally. If unusual resistance is felt during product mandrel and stent sheath removal, do not use this product and replace with another. Follow product returns procedure for the unused device.

#### 13.3.2 Guide Wire Lumen Flush

1. Over the Wire (OTW) only: Flush the guide wire lumen with HepNS until fluid exits the distal end of the delivery system.
2. Rapid Exchange (RX) only: Flush the guide wire lumen with HepNS using the flushing tool supplied with the product. Insert the flushing tool into the tip of the catheter and flush until fluid exits the guide wire exit notch.

**Note:** Avoid manipulation of the stent while flushing the guide wire lumen, as this may disrupt the placement of the stent on the balloon.

### 13.3.3 Delivery System Preparation

1. Prepare an inflation device/syringe with diluted contrast medium.
2. Attach an inflation device/syringe to the stopcock; attach it to the inflation port of the product. Do not bend the product hypotube when connecting to the inflation device/syringe.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to delivery system; pull negative for 30 seconds; release to neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device/syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.
7. If a syringe was used, attach a prepared inflation device to stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral

**Note:** If air is seen in the shaft, repeat Delivery System Preparation steps 3 through 5 to prevent uneven stent expansion.

### 13.4 Delivery Procedure

1. Prepare the vascular access site according to standard practice.
2. **Pre-dilate the lesion with a PTCA catheter of appropriate length and diameter for the vessel/lesion to be treated.** Limit the longitudinal length of pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the PROMUS Stent.

**Note:** The labeled stent diameter refers to expanded stent inner diameter.

3. Maintain neutral pressure on the inflation device attached to the delivery system. Open the rotating hemostatic valve as wide as possible.
4. Backload the delivery system onto the proximal portion of the guide wire while maintaining guide wire position across the target lesion.
5. Carefully advance the delivery system into the guiding catheter and over the guide wire to the target lesion. When using a Rapid Exchange (RX) system be sure to keep the hypotube straight. Ensure guiding catheter stability before advancing the stent system into the coronary artery.

**Note:** If unusual resistance is felt before the stent exits the guiding catheter, do not force passage. Resistance may indicate a problem and the use of excessive force may result in stent damage or dislodgement. Maintain guide wire placement across the lesion and remove the delivery system and guiding catheter as a single unit.

6. Advance the delivery system over the guide wire to the target lesion under direct fluoroscopic visualization. Utilize the radiopaque balloon markers to position the stent across the lesion. Perform angiography to confirm stent position. If the position of the stent is not optimal, it should be carefully repositioned or removed (see Section 5.14 – Precautions, Delivery System Removal). The balloon markers indicate both the stent edges and the balloon shoulders. Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion.

**Note:** Should any resistance be felt at any time during either lesion access or removal of the delivery system post-stent implantation, remove the entire system as a single unit. See Section 5.14 – Precautions, Delivery System Removal for specific delivery system removal instructions.

7. Tighten the rotating hemostatic valve. The stent is now ready to be deployed.

### 13.5 Deployment Procedure

**CAUTION:** Refer to Table 14-1: Typical PROMUS Stent Compliance for in vitro stent inner diameter, nominal pressure, and RBP.

1. Prior to deployment, reconfirm the correct position of the stent relative to the target lesion using the radiopaque balloon markers.
2. Deploy the stent slowly by pressurizing the delivery system in 2 atm increments, every 5 seconds, until stent is completely expanded. Accepted practice generally targets an initial deployment pressure that would achieve a stent inner diameter ratio of about 1.1 times the reference vessel diameter (see Table 14-1). Maintain pressure for 30 seconds. If necessary, the delivery system can be repressurized or further pressurized to assure complete apposition of the stent to the artery wall. **Do not exceed the labeled rated burst pressure (RBP) of 16 atm (1.62 MPa).**
3. Fully cover the entire lesion and balloon treated area (including dissections) with the PROMUS stent, allowing for adequate stent coverage into healthy tissue proximal and distal to the lesion.
4. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to guiding catheter position.
5. Confirm stent position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the stent. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the artery wall. Stent wall contact should be verified through routine angiography or intravascular ultrasound (IVUS).
6. If the deployed stent size is still inadequate with respect to reference vessel diameter, a larger balloon may be used to further expand the stent. If the initial angiographic appearance is sub-optimal, the stent may be further expanded using a low profile, high pressure, non-compliant balloon dilatation catheter. If this is required, the stented segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the stent geometry. Deployed stents should not be left under-dilated.

**CAUTION:** Do not dilate the stent beyond the following limits.

<u>Nominal Stent Diameter</u>	<u>Dilatation Limit</u>
2.5 mm to 3.0 mm	3.5 mm
3.5 mm to 4.0 mm	4.5 mm

7. If more than one PROMUS stent is needed to cover the lesion and balloon treated area, it is suggested that, to avoid the potential for gap restenosis, the stents be adequately overlapped. To ensure that there are no gaps between

stents the balloon marker bands of the second PROMUS stent should be positioned inside the deployed stent prior to expansion.

8. Reconfirm stent position and angiographic results. Repeat inflations until optimal stent deployment is achieved.

### 13.6 Removal Procedure

1. Deflate the balloon by pulling negative pressure on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during stent delivery system withdrawal, pay particular attention to the guiding catheter position.
  2. Fully open the rotating hemostatic valve.
  3. While maintaining the guide wire position and negative pressure on the inflation device, withdraw the delivery system.
- Note:** Should **any resistance** be felt at **any time** during either lesion access or removal of the delivery system post-stent implantation, the entire system should be **removed as a single unit**. See Section 5.14 – Precautions, Delivery System Removal for specific delivery system removal instructions.
4. Tighten the rotating hemostatic valve.
  5. Repeat angiography to assess the stented area. If post-dilatation is necessary, ensure that the final stent diameter matches the reference vessel diameter. **Assure that the stent is not under-dilated.**

### 13.7 Post-Deployment Dilatation of Stent Segments

1. All efforts should be taken to assure that the stent is not underdilated. If the deployed stent size is still inadequate with respect to the vessel diameter, or if full contact with the vessel wall is not achieved, a larger balloon may be used to expand the stent further. The stent may be further expanded using a low profile, high pressure, and non-compliant balloon catheter. If this is required, the stented segment should be recrossed carefully with a prolapsed guide wire to avoid dislodging the stent. The balloon should be centered within the stent and should not extend outside of the stented region.

**CAUTION:** Do not dilate the stent beyond the following limits.

<u>Nominal Stent Diameter</u>	<u>Dilatation Limit</u>
2.5 mm to 3.0 mm	3.5 mm
3.5 mm to 4.0 mm	4.5 mm

## 14.0 IN VITRO COMPLIANCE INFORMATION

**Table 14-1: Typical PROMUS Stent Compliance**  
Nominal pressure for each diameter indicated by bold font.

Pressure		Stent ID (mm) by System Size				
(atm)	(MPa)	2.5 mm	2.75 mm	3.0 mm	3.5 mm	4.0 mm
8	0.81	<b>2.46</b>	<b>2.74</b>	2.90	3.46	3.86
9	0.91	2.52	2.81	<b>2.97</b>	<b>3.55</b>	<b>3.95</b>
10	1.01	2.58	2.87	3.04	3.63	4.03
11	1.11	2.63	2.92	3.10	3.69	4.10
12	1.22	2.68	2.97	3.15	3.75	4.17
13	1.32	2.72	3.01	3.19	3.80	4.23
14	1.42	2.75	3.05	3.23	3.84	4.28
15	1.52	2.78	3.08	3.26	3.89	4.33
16 (RBP)*	1.62	<b>2.81</b>	<b>3.11</b>	<b>3.30</b>	<b>3.93</b>	<b>4.37</b>
17	1.72	2.84	3.14	3.33	3.97	4.42
18	1.82	2.87	3.18	3.36	4.00	4.46

Note: These nominal data are based on *in vitro* testing at 37°C and do not take into account lesion resistance.

Ensure full deployment of the stent (see Section 13.5, Operator's Instructions, Deployment Procedure) and confirm the stent sizing angiographically.

\*Do not exceed the rated burst pressure (RBP).

## 15.0 REUSE PRECAUTION STATEMENT

Do not use if sterile barrier is damaged. If damage is found call your Boston Scientific, Cardiac Therapies representative.

For single patient use only. Do not reuse, reprocess or resterilize.

## 16.0 PATENTS

This product and its use are protected by one or more of the following patents. United States, 4,571,240; 4,573,470; 4,581,017; 4,582,181; 4,597,755; 4,616,653; 4,619,263; 4,638,805; 4,641,654; 4,661,094; 4,664,113; 4,692,200; 4,748,982; 4,771,776; 4,771,777; 4,771,778; 4,775,371; 4,782,834; 4,790,315; 4,793,350; 4,821,722; 4,877,031; 4,892,519; 4,938,220; 4,940,062; 4,964,409; 4,976,720; 4,981,478; 4,998,917; 4,998,923; 5,002,532; 5,002,560; 5,003,989; 5,034,001; 5,040,548; 5,042,985; 5,046,503; 5,061,273; 5,090,959; 5,135,535; 5,137,513; 5,154,725; 5,159,937; 5,176,661; 5,180,368; 5,195,971; 5,234,002; 5,242,394; 5,242,396; 5,256,143; 5,263,963; 5,279,562; 5,290,230; 5,300,025; 5,300,085; 5,316,706; 5,318,527; 5,324,259; 5,334,154; 5,342,621; 5,346,505; 5,348,537; 5,350,395; 5,391,172; 5,397,305; 5,409,495; 5,411,476; 5,415,637; 5,421,955; 5,423,755; 5,423,885; 5,437,083; 5,441,515; 5,443,458; 5,443,500; 5,451,209; 5,451,233; 5,456,667; 5,458,605; 5,458,613; 5,458,615; 5,476,505; 5,480,383; 5,496,275; 5,496,346; 5,498,240; 5,507,301; 5,507,768; 5,507,795; 5,514,154; 5,516,336; 5,525,388; 5,533,968; 5,542,925; 5,546,646; 5,549,551; 5,549,554; 5,554,120; 5,554,121; 5,556,413; 5,558,643; 5,565,523; 5,573,508; 5,573,509; 5,591,197; 5,593,434; 5,603,721; 5,605,696; 5,607,444; 5,618,299; 5,629,077; 5,632,754; 5,632,840; 5,636,641; 5,637,089; 5,637,113; 5,649,977; 5,681,346; 5,693,015; 5,695,506; 5,700,286; 5,707,385; 5,709,658; 5,725,549; 5,728,158; 5,735,893; 5,743,875; 5,747,591; 5,749,888; 5,759,192; 5,769,868; 5,780,807; 5,782,855; 5,807,355; 5,816,923; 5,830,181; 5,849,846; 5,868,706; 5,868,767; 5,891,090; 5,902,290; 5,931,819; 5,989,218; 5,993,460; 6,013,054; 6,013,069; 6,013,728; 6,017,364; 6,019,777; 6,027,475; 6,036,707; 6,036,715;

6,056,776; 6,059,748; 6,059,770; 6,061,588; 6,117,106; 6,126,634; 6,126,635; 6,129,707; 6,131,266; 6,136,011; 6,139,525; 6,156,047; 6,165,152; 6,165,292; 6,179,810; 6,193,686; 6,200,325 B1; 6,206,852; 6,217,547; 6,221,425; 6,224,803; 6,238,376; 6,248,092; 6,251,094; 6,273,911; 6,296,655; 6,299,595; 6,309,412; 6,369,355; 6,419,693; 6,432,133; 6,482,166; 6,485,511; 6,488,655; 6,488,694; 6,527,789; 6,561,788; 6,572,813; 6,575,958; 6,575,993; 6,620,193; 6,629,991; RE 33,166; RE 34,564.

Other U.S. patents pending. Foreign patents issued and pending.

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Boston Scientific Corporation (BSC) warrants that reasonable care has been used in the design and manufacture of this instrument. **This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties of merchantability or fitness for a particular purpose.** Handling, storage, cleaning and sterilization of this instrument as well as other factors relating to the patient, diagnosis, treatment, surgical procedures, and other matters beyond BSC's control directly affect the instrument and the results obtained from its use. BSC's obligation under this warranty is limited to the repair or replacement of this instrument and BSC shall not be liable for any incidental or consequential loss, damage, or expense directly or indirectly arising from the use of this instrument. BSC neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this instrument. **BSC assumes no liability with respect to instruments reused, reprocessed or resterilized and makes no warranties, express or implied, including but not limited to merchantability or fitness for a particular purpose, with respect to such instruments.**

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**Abbott Vascular**  
Santa Clara, CA 95054-2807 USA

**CUSTOMER SERVICE**  
TEL: (800) 227-9902  
FAX: (800) 601-8874  
Outside USA TEL: (951) 914-4669  
Outside USA FAX: (951) 914-2531

**Boston  
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One Boston Scientific Place  
Natick, MA 01760-1537 USA

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**Graphical Symbols for Medical Device Labeling**

Manufacturer	REF Catalogue Number	F French Size
 Do not reuse, do not sterilize	<b>STERILE EO</b> Sterilized using Ethylene Oxide	 Consult Instructions for Use
 Use By	<b>LOT</b> Batch Code	 Date of Manufacture
 Guiding Catheter	 <b>pyrogenic</b> Non-Pyrogenic	 Contents (Numerical represents quantity of units inside)
 Outer Diameter		

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